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Development of Transition Metal Catalyzed Carbon-Carbon Bond Forming Reactions with Abundant or Scarce Chemicals

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Development of Transition Metal Catalyzed Carbon-Carbon Bond Forming Reactions with Abundant or Scarce Chemicals

by

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Dedication

To my family

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Development of Transition Metal Catalyzed Carbon-Carbon Bond Forming Reactions with Abundant or Scarce Chemicals

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The development of more efficient carbon-carbon bond transformation is of great significance. One of the more common approaches to forging carbon-carbon bonds is the addition of carbon- based nucleophiles to carbonyl compounds, exploiting classical electrophile-nucleophile pairing. In an effort to minimize nucleophile pre-activation and organometallic byproducts, my research in the Krische group focuses on the development of efficient methods for the *in*-situ formation of alkyl-metal nucleophiles from π-unsaturated compounds *via* transition metal catalysis. With the use of Ruthenium or Osmium we can use readily abundant α-olefins such as ethylene gas and couple it with various secondary alcohols via transfer hydrogenative C-C coupling in a proposed oxidative coupling pathway.

Table of Contents

List of Tables xi

List of Figures xiv

List of Schemes xvi

Chapter 1: Metal Catalyzed C-C Coupling of Alpha Olefins Beyond Hydroformylation 1

1.1 Introduction 1

1.2 C-H Activation 2

1.2.1 Ruthenium Catalyzed C-H Activation 2

1.2.2 Tantalum Catalyzed C-H Activation 3

1.2.3 Iridium Catalyzed C-H Activation 6

1.2.4 Scandium Catalyzed C-H Activation 8

1.2.5 Nickel Catalyzed C-H Activation 11

1.2.6 Iron Catalyzed C-H Activation 15

1.3 Carbonyl Addition 16

1.3.1 Nickel Catalyzed Carbonyl Addition 16

1.3.2 Ruthenium Catalyzed Carbonyl Addition 21

1.3.3 Osmium Catalyzed Carbonyl Addition 21

1.3.4 Iron Catalyzed Carbonyl Addition 23

1.4 Cross Coupling 24

1.4.1 Nickel Catalyzed Cross Coupling 24

1.4.2 Platinum and Palladium Catalyzed Cross Coupling 29

1.5 Cyclopropanation 31

1.5.1 Iridium Catalyzed Cyclopropanation 31

1.6 Conclusion 32

Chapter 2: Ruthenium Catalyzed C-C Coupling of α-Olefins and Styrenes to 3-Hydroxy-2-Oxindoles 34

2.1 Introduction 34

2.2 Background and Reaction Development 35

2.3 Proposed Mechanism 38
2.4 Reaction Scope....40
2.5 Conclusion 43
2.6 Experimental Section 43

Chapter 3: Osmium Catalyzed C-C Coupling of α-Olefins to Diols, Ketols or Hydroxy Esters....121
3.1 Background 121
3.2 Reaction Development....121
3.3 Proposed Mechanism 123
3.4 Reaction Scope....126
3.5 Conclusion 132
3.6 Experimental Section 133

Chapter 4: Vinyl Transfer from Enol Carboxylates via Transition Metal Catalysis by way of Metallacycle Fragmentation....241
4.1 Introduction....241
4.2 Reaction Development and Scope 242
4.3 Proposed Mechanism 247
4.4 Conclusion 248
4.5 Experimental Section 249

Chapter 5: Ruthenium Catalyzed C-C Coupling of Alkynes to 3-Hydroxy-2-Oxindoles 338
5.1 Introduction....338
5.2. Reaction Development and Scope 338
5.3 Conclusion 342
5.4 Experimental Section 343

Chapter 6: Transition Metal Catalyzed Couplings of Organofluorine Compounds via Transfer Hydrogenation 423
6.1 Introduction....423
6.2 Background 424
6.3 Reaction Development....425

6.4 Proposed Mechanism 426
6.5 Reaction Scope 429
6.6 Conclusion 430
6.7 Experimental Section 431
References 537

List of Tables

Table 1.1: Hydroaminoalkylation using various early metal dimethylamido complexes 4

Table 1.2: Select examples of Ta catalyzed hydroaminoalkylation 5

Table 1.3: Reactivity based on Ta catalyst precursor 6

Table 1.4: Select examples of Ir catalyzed olefination of furans 7

Table 1.5: Select examples of Sc catalyzed alkylation with various pyridines 9

Table 1.6: Select examples of Sc catalyzed alkylation with various α-olefins 10

Table 1.7: Select examples of Ni catalyzed alkylation of electron deficient arenes with various α-olefins 12

Table 1.8: Select examples of Ni catalyzed alkylation of benzoheteroarenes 14

Table 1.9: Select examples of Ni catalyzed alkylation of heteroarenes 14

Table 1.10: Select examples of Fe catalyzed sulfur directed alkylation 15

Table 1.11: Select examples of Ni catalyzed carbonyl addition using α-olefins 17

Table 1.12: Select examples of Ni catalyzed carbonyl-ene reaction with α-olefins 18

Table 1.13: Select examples of Ni catalyzed coupling of α-olefins with isocyanates 19

Table 1.14: Select examples of Ni catalyzed conjugate addition with α-olefins 20

Table 1.15: Select examples of Ru catalyzed hydrohydroxyalkylation 21

Table 1.16: Select examples of Os catalyzed hydrohydroxyalkylation of hydroxy esters 22

Table 1.17: Select examples of Os catalyzed hydrohydroxyalkylation of α-ketols 22

Table 1.18: Select examples of Os catalyzed hydrohydroxyalkylation of 1,2-diols 23

Table 1.19: Select examples of Fe catalyzed carbonyl addition 24

Table 1.20: Select examples of Ni catalyzed cross-coupling using benzyl chlorides and ethylene gas 25
Table 1.21: Select examples of Ni catalyzed cross-coupling using benzyl chlorides and higher order alkenes 26
Table 1.22: Select examples of Ni catalyzed cross-coupling using aryl sulfonates and 1-octene 27
Table 1.23: Select examples of Ni catalyzed HAT using iodoarenes and alkenes29
Table 1.24: Select examples of Pt/Pd catalyzed cross coupling using alkenes and aryl halides 30
Table 1.25: Select examples of Pt/Pd catalyzed cross coupling using alkenes and alkyl halides 30
Table 1.26: Select examples of Ir salen catalyzed cyclopropanation with alkenes31
Table 1.27: Select examples of Ir salen catalyzed cyclopropanation with alkenes32
Table 2.1: Optimization for amount of styrene 37
Table 2.2: Coupling of α-olefins to *N*-benzyl-3-hydroxy-2-oxindoles.....41
Table 2.3: Coupling of styrene derivatives with *N*-benzyl-3-hydroxy-2-oxindoles42
Table 3.1: Selected examples for the catalytic system optimization between ethyl mandelate and ethylene 123
Table 3.2: Coupling of ethylene with ethyl mandelate derivatives 127
Table 3.3: Coupling of ethylene with α-ketol derivatives 128
Table 3.4: Coupling of ethylene with 1,2-diol derivatives.....129
Table 3.5: Coupling of 1-octene with α-hydroxy esters and ketols 130
Table 3.6: Coupling of ethyl mandelate with functionalized olefins 130
Table 3.7: Coupling of 1-octene with different oxidation states of acenaphthenequinone 132

Table 4.1: Osmium-catalyzed vinyl transfer to α-ketoester.....245

Table 4.2: Ruthenium-catalyzed vinyl transfer to *N*-benzyl-3-hydroxy-2-oxindoles 246

Table 4.3: Osmium-catalyzed vinyl transfer to 1,2-diols.....247

Table 5.1: Selected optimization experiments for 1-phenyl-1-butyne coupling with *N*-benzyl-3-hydroxy-2-oxindole 339

Table 5.2: Ruthenium-catalyzed coupling of alkynes to *N*-benzyl-3-hydroxy-2-oxindoles.....340

Table 5.3: Ruthenium-catalyzed coupling of 1-phenylpropyne to substituted *N*-benzyl-3-hydroxy-2-oxindoles.....341

Table 6.1: Examples of ruthenium catalyzed hydrohydroxyfluoroalkylation.....429

List of Figures

Figure 1.1: Proposed mechanistic pathway of hydroaminoalkylation 4

Figure 1.2: C-H activation aromatic ketones followed by C-C bond formation....6

Figure 1.3: Plausible mechanism for Ir catalyzed olefination of furans 8

Figure 1.4: Plausible mechanism for Sc catalyzed alkylation of pyridines 11

Figure 1.5: Select examples of Ni NHC catalysts.....13

Figure 1.6: Plausible mechanism for Fe catalyzed sulfur directed alkylation 16

Figure 1.7: Rationale of regioselectivity for acrylamide products.....19

Figure 1.8: Plausible mechanism for Ni catalyzed conjugate addition of enones20

Figure 1.9: Plausible Ni catalyzed benzylation using benzyl chlorides.....27

Figure 1.10: Steric effects on Ni catalyzed cross-coupling of aryl sulfonates.....28

Figure 2.1: Catalytic mechanisms *via* hydrogenation or transfer hydrogenation .35

Figure 2.2: Screen of different acid co-catalysts.....36

Figure 2.3: Possible cleavage transition states of the oxaruthenacycle 37

Figure 2.4: Proposed catalytic mechanism for *N*-benzyl-3-hydroxy-2-oxindole and ethylene.....39

Figure 2.5: Proposed stereochemical model for observed *anti*-diastereomer between styrene and *N*-benzyl-3-hydroxy-2-oxindole.....40

Figure 3.1: Crystal structure of $Os_2(CO)_4(O_2CR)_2(XPhos)_2$ 124

Figure 3.2: Crystal structure of $Os_3(CO)_{11}(XPhos)$ 124

Figure 3.3: Proposed catalytic mechanism for ethyl mandelate and 1-octene..125

Figure 4.1: Proposed catalytic mechanism for metal catalyzed metallacycle fragmentation.....248

Figure 6.1: Selected examples of organofluorine compounds 423

Figure 6.2: Prices for selected fluorinated aldehydes and alcohol congeners 424

Figure 6.3: Initial probe of the limits of fluorinated alcohols 426

Figure 6.4: Proposed mechanism of fluorinated alcohol coupling with allenes .427

List of Schemes

Scheme 1.1: C-H activation of aryl ketones followed by C-C bond formation 2

Scheme 1.2: Select examples of Ru catalyzed C-H activation with various ketones3

Scheme 1.3: Select examples of Ru catalyzed C-H activation with terminal olefins 3

Scheme 1.4: Plausible MVP mechanism for Fe catalyzed carbonyl addition 24

Scheme 1.5: Plausible 1,5-H Shift mechanism for Fe catalyzed carbonyl addition24

Scheme 1.6: Cyclopropanation of 1,5 and 1,6 dienes 32

Scheme 2.1: Effect of acid co-catalyst between *N*-benzyl-3-hydroxy-2-oxindole and propylene.....36

Scheme 2.2: Coupling of styrene with 3-hydroxy-2-oxindole 43

Scheme 3.1: Deuterium labeling experiments with *deuterio*-**3.3k**.....126

Scheme 4.1: Metal catalyzed vinyl transfer processes 241

Scheme 4.2: Catalytic metal catalyzed vinyl transfer *via* metallacycle fragmentation 242

Scheme 4.3: Selected optimization experiments for vinyl transfer using ethyl mandelate 243

Scheme 4.4: Conjugate enones as vinyl transfer reagents to *N*-benzyl-3-hydroxy-2-oxindoles 246

Scheme 4.5: Ruthenium-catalyzed vinyl transfer to *N*-benzyl-isatin 246

Scheme 5.1: Coupling of aryl alkynes to 1,2-diols 338

Scheme 5.2: Product elaborations of **5.3a** 342

Scheme 6.1: Inductive fluoroalkyl moieties and its effect on β-hydride elimination 425

Scheme 6.2: Competition kinetics studies with *deuterio*-3,3,3-trifluoropropanol428

Scheme 6.3: Competition kinetics studies with *deuterio*-4,4,4-trifluorobutanol 428

Scheme 6.4: Conversion of product **6.3n** to CF_3-containing amino acid.....430

Chapter 1: Metal Catalyzed C-C Coupling of Alpha Olefins Beyond Hydroformylation

1.1 Introduction

The most abundant petrochemical feedstock next to alkanes are α-olefins.[1] α-olefins come from petroleum cracking and can be described as the process of breaking down longer chain hydrocarbons to smaller fragments providing alkanes and alkenes. α-olefins are also known as alkenes with a chemical formula C_xH_{2x}. A distinct feature of α-olefins is that they bear the double bond at the beginning of their chemical chain and can be designated as the alpha (α) position. The use of α-olefins is mostly focused in the area of chemical manufacturing, specifically in polymerization[2] and hydroformylation[3], also known as the oxo-process. The importance of α-olefins can be seen in its use in hydroformylation, being one of the top two homogenous metal catalyzed processes in the world, providing aldehyde building blocks.[4] It would be advantageous to use α-olefins to synthesize new carbon-carbon bonds beyond the products of hydroformylation and take advantage of such a abundant chemical feedstock.

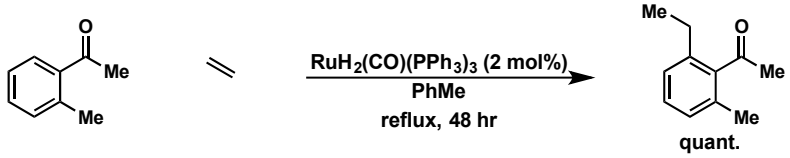
This review aims to provide a snapshot of the advancements in chemical synthesis using α-olefins to provide value added products. The review is divided up into four major sections: C-H activation, carbonyl addition, cross-coupling and cyclopropanation reactions.

1.2 C-H ACTIVATION

1.2.1 Ruthenium Catalyzed C-H Activation

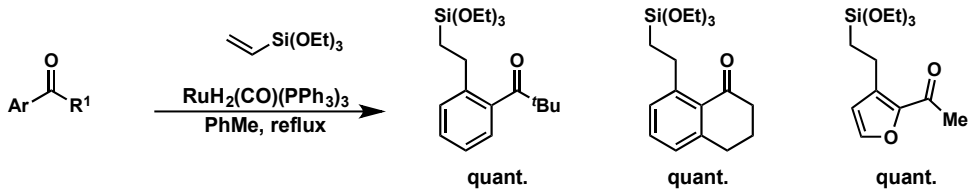
One of the earliest reports of a metal catalyzed C-C coupling of an α-Olefin involved the use of a zirconium based catalyst coupling propylene gas with α-picoline reported by Taylor and co-workers.[5] The zirconium based reaction provides high yields but fall short due to its generality, leaving one only limited to α-picoline as the coupling partner. A handful of years later Murai and co-workers discovered that by subjecting a ruthenium based catalyst, an aryl ketone and a terminal olefin, the product of C-C coupling could be formed. It is described that in the reaction the aromatic ortho C-H bond would be substituted and a new C-C bond is forged (**Scheme 1.1**). [6]

Scheme 1.1: C-H activation of aryl ketones followed by C-C bond formation

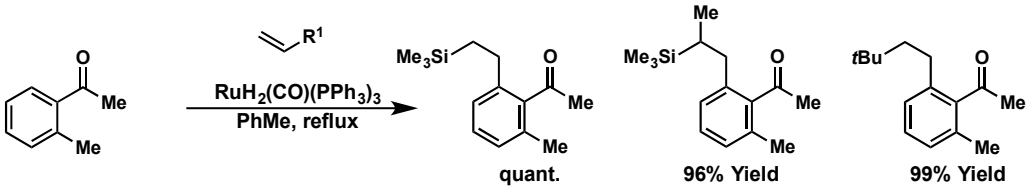


This reaction allowed the formation of a new C-C bond with high levels of efficiency and selectivity. Murai credited the success of the reaction was due to chelation. The carbonyl group coordinates with the low-valent ruthenium metal which then positions the metal to insert itself in between the C-H bond of the aromatic system followed by subsequent C-C bond formation. Various aromatic ketones and olefins were examined to test the extent of the reaction (**Scheme 1.2** and **1.3**). Gratifyingly in most cases the reaction provided the desired coupling product in nearly quantitative yield. The reaction was also tolerant of acylheteroaromatics and mono- and di-substituted terminal olefins.

Scheme 1.2: Select examples of Ru catalyzed C-H activation with various ketones



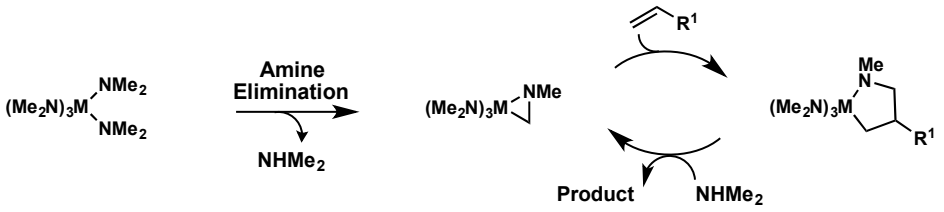
Scheme 1.3: Select examples of Ru catalyzed C-H activation with terminal olefins



1.2.2 Tantalum Catalyzed C-H Activation

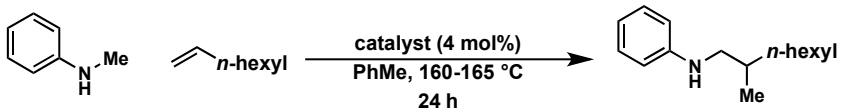
Maspero and co-workers reported the α-alkylation of dimethylamine with simple terminal olefins in the presence of a tantalum catalyst. Products of alkylation were obtained providing exclusively the branched product but was stifled with poor yields, 38% and long reaction times (1 week), using 1-hexene.[7] It has been shown by Holmes and Sugiyama that the addition of these unactivated olefins occur by way of a η^2-imine complex resulting in a new M-C bond (**Figure 1.1**).[8,9] In related work, Whitby and co-workers observed that by using *N*-aryl alkylamines η^2-imine complexes form faster compared to their dialkylamido counterparts.[10] Hartwig and co-workers hypothesized that by using *N*-aryl alkylamines, product of hydroaminoalkylation would proceed more readily.[11]

Figure 1.1: Proposed mechanistic pathway of hydroaminoalkylation



Consistent with all the work shown above, Hartwig and co-workers was able to obtain the product of hydroaminoalkylation providing the branched product exclusively, using *N*-methylaniline with 1-octene in the presence of a tantalum catalyst. Hartwig and co-workers surveyed a variety of early metal dimethylamido complexes, but the $Ta(NEt_2)_5$ was shown to be the best (**Table 1.1**).

Table 1.1: Hydroaminoalkylation using various early metal dimethylamido complexes

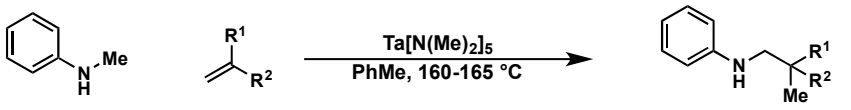


Entry	Catalyst Precursor	Yield (%)
1	$Ta[N(Me)_2]_5$	96
2	$Ta[N(Et)_2]_5$	66
3	$Nb[N(Me)_2]_5$	35
4	$Cp_2Zr[N(Me)_2]_5$	3
5	none	0

It is noted that by using identical conditions with *N*-methylacetamide and *N*-methylsulfonamide derivatives give only trace amount of product. However, the use of mono- and di-substituted olefins were tolerated with *N*-methylaniline (**Table 1.2**). Not being

limited to just the parent *N*-methylaniline, substitution on the aromatic ring and 1,2,3,4-tetrahydroquinoline were also tolerated in the reaction.

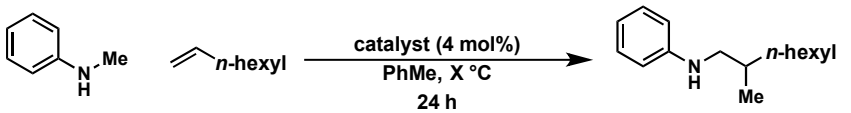
Table 1.2: Select examples of Ta catalyzed hydroaminoalkylation



Entry	R^1	R^2	Mol% Ta	Yield (%)
1	H	*n*-hexyl	4	88
2	H	$SiPh(Me)_2$	4	50
3	H	CH_2Ph	4	77
4	Me	*n*-pentyl	8	76
5			4	71

In the following year, Hartwig and co-workers described a procedure where the products of hydroaminoalkylation of unactivated olefins can now be achieved with dialkylamines.[12] The key to getting the dialkylamines to work was the use of a chlorotantalum amide catalyst that displayed greater reactivity. The use of such catalyst allowed Hartwig and co-workers to perform the same reaction involving a *N*-alkyl-arylamine at much milder conditions (**Table 1. 3**).

Table 1.3: Reactivity based on Ta catalyst precursor



Entry	Catalyst Precursor	T (°C)	Yield (%)
1	$Ta[N(Me)_2]_5$	160	96
2	$Ta[N(Me)_2]_5$	90	0
3	$[Cl_3Ta(NMePh)_2]_2$	90	72

1.2.3 Iridium Catalyzed C-H Activation

Hartwig and co-workers reported the olefination of furans with unactivated alkenes, using an iridium catalyst.[13] The resting state of the catalyst was different depending on temperature, at 50°C the catalyst was the Ir(olefin) complex **I** and at 130°C was a Ir(allyl)H complex **II** (**Figure 1.2**). With these mechanistic findings, the preparation of electronically deficient and bulkier DTBM-SEGPHOS based ligands in hopes of reducing the rate of allylic C-H activation and dimerization of the catalyst.

Figure 1.2: C-H activation aromatic ketones followed by C-C bond formation

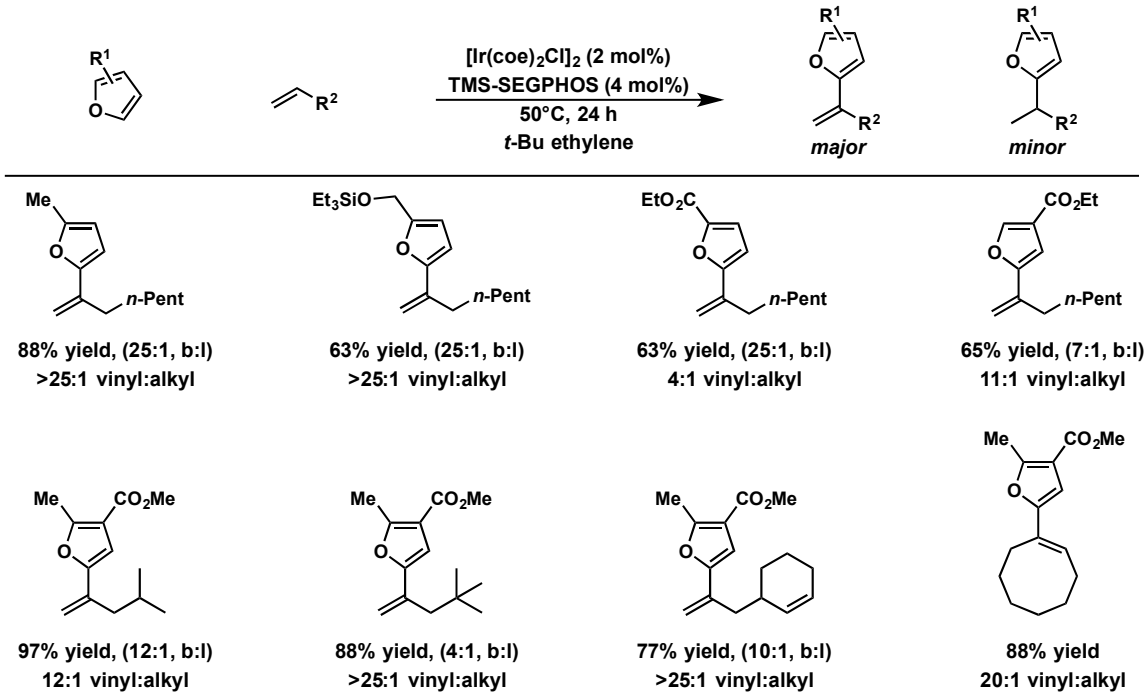
I
Resting State at 50°C

II
Resting State at 130°C

It was found that SEGPHOS derivatives containing 3,5-bis-(trialkylsilyl) arenes provided the best results in terms of yield and the minimization of hydrogenated vinylfuran products. With the TMS-SEGPHOS racemate in hand, the reaction conditions were well suited for a variety of mono- and di-substituted furans and acyclic or cyclic olefins (**Table**

1.4). Electron rich furans such as 2-methylfuran was obtained in higher yields in comparison to the electron deficient furans such as ethyl 2-furoate. In the case of substitution at the C2 and C3 position of the furan, reactivity was more comparable to the 2-methylfuran over the ethyl 2-furoate thus suggesting that coupling at the C5 position is strongly influenced by the C2 substituent.

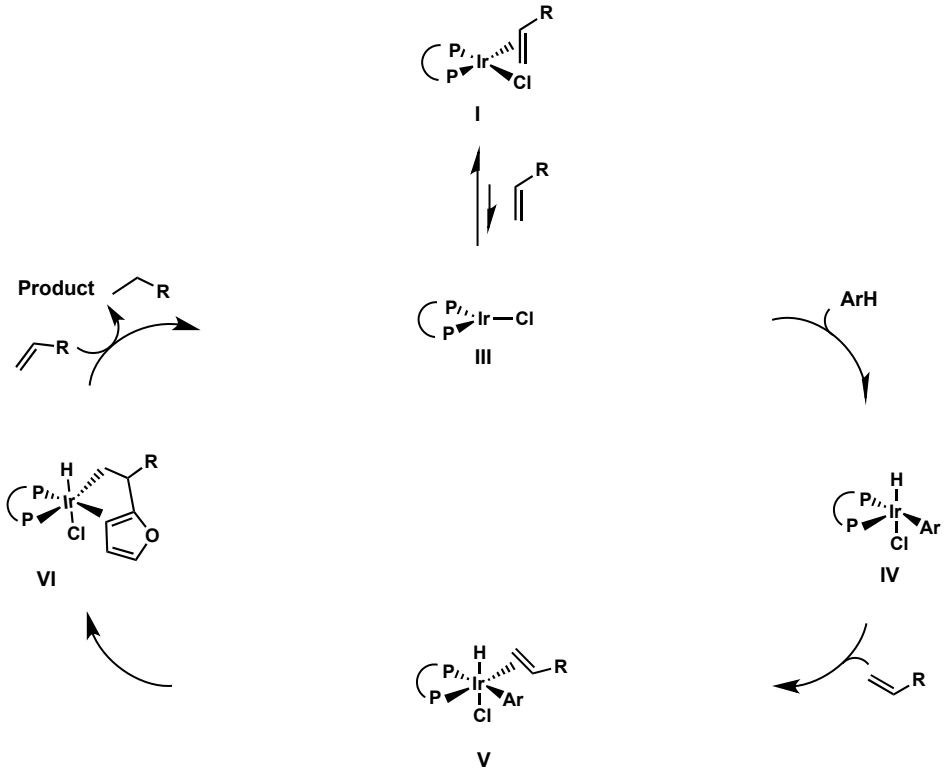
Table 1.4: Select examples of Ir catalyzed olefination of furans



A plausible mechanism starts with the iridium olefin complex **I** having the olefin dissociate to form complex **III**. Oxidative addition then occurs with the furan to form the furyliridium hydride complex **IV** which then coordinates with your alkene providing you with complex **V**. Insertion of the alkene provides intermediate **VI** followed by β-H

elimination releasing the product and hydrogenation of the hydrogen acceptor regenerates complex **III**, closing the catalytic cycle (**Figure 1.3**).

Figure 1.3: Plausible mechanism for Ir catalyzed olefination of furans



1.2.4 Scandium Catalyzed C-H Activation

Pyridines being one of the most important heterocyclic moieties in natural products, pharmaceuticals and ligands have had a lack of methods in C-H bond functionalization.[14,15,16] In 1994 Rodewald and Jordan reported the use of a zirconocene based catalyst to promote C-H bond functionalization between picoline and 1-hexene.[17] Hou and co-workers report that with the use of chiral half-sandwich scandium complexes the alkylation of pyridines using α-olefins can be achieved. A variety of pyridine derivatives are tolerated such as mono- and di-

substituted pyridines.[18] Pyridines baring a halogen was also tolerated within the reaction conditions providing a useful functional handle for further manipulation. Not being limited to just pyridines, tetrahydroquinoline and 2,3-cyclopentenopyridine were also tolerated within the reaction conditions (**Table 1.5**). To further evaluate the applicability of the reaction, a variety of α-olefins were also tested and proceeded smoothly to provide products in good yield and enantioselectivity (**Table 1.6**).

Table 1.5: Select examples of Sc catalyzed alkylation with various pyridines

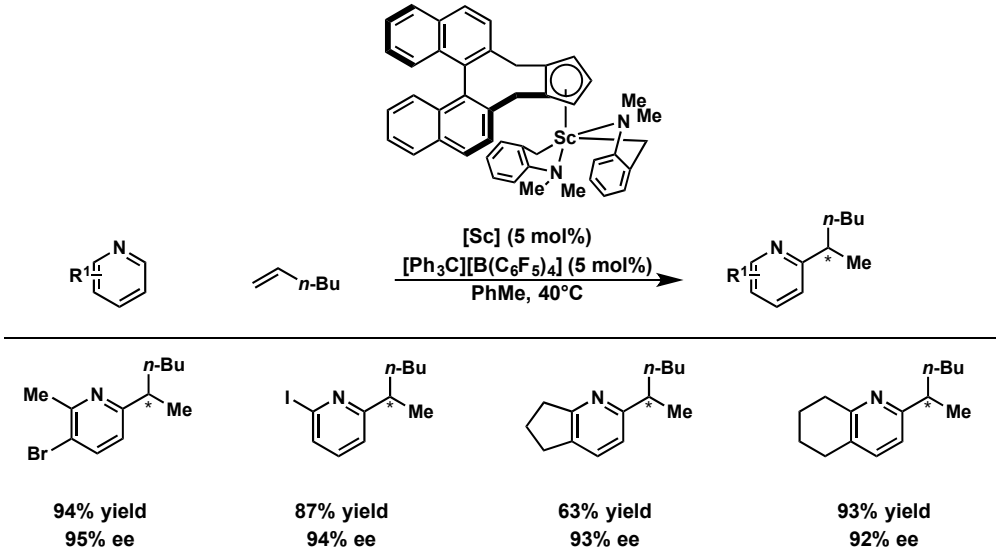
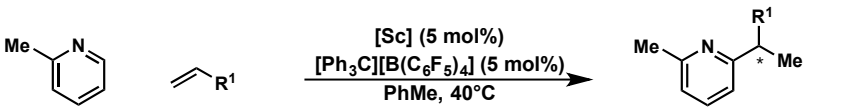


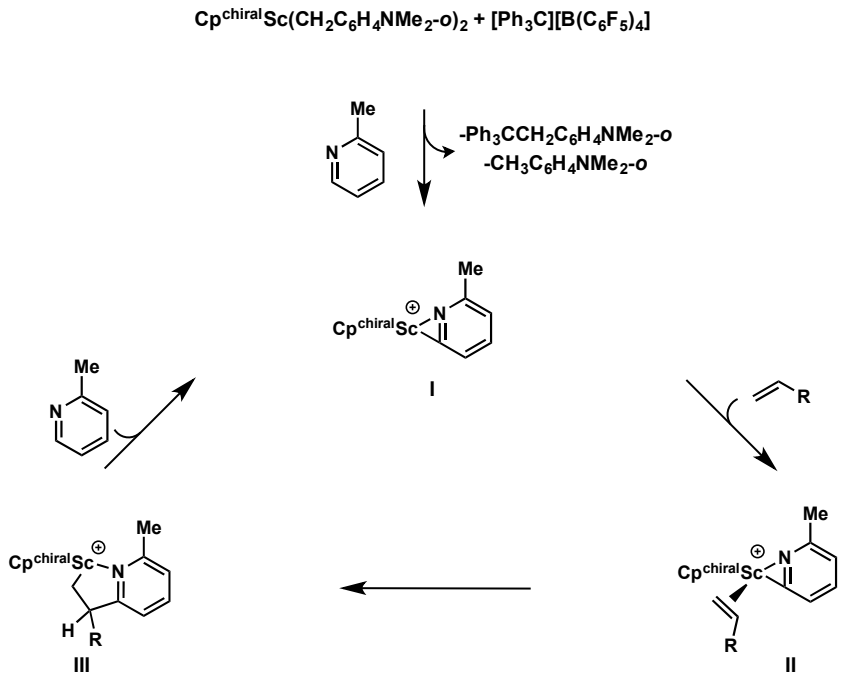
Table 1.6: Select examples of Sc catalyzed alkylation with various α-olefins



Entry	R^1	Yield (%)	ee (%)
1	*n*-C_5H_{11}	92	93
2	*n*-C_6H_{13}	92	93
3	$CH_2CH(CH_3)_2$	95	90
4	$CH_2(C_6H_{11})$	94	91
5	$CH_2Si(Me)_3$	80	86

A possible reaction mechanism proposed by the authors for the alkylation of these pyridine systems is that the formation of the η^2-pyridyl species (I) could possibly come from the deprotonation of 2-picoline at the C6 position with the cationic Sc benzyl species. This cationic species comes from the reaction of Hou's scandium catalyst being treated with the $[Ph_3C][B(C_6F_5)_4]$ salt. Then upon coordination with the olefin **II**, addition occurs giving intermediate **III**, followed by protonation releases the product of alkylation (**Figure 1.4**).

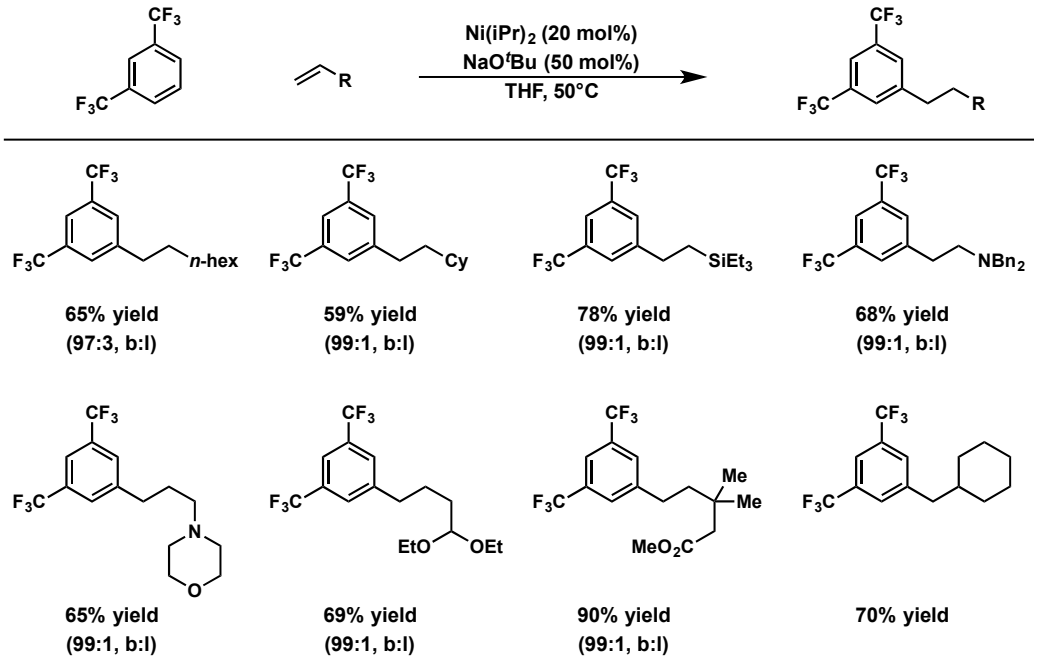
Figure 1.4: Plausible mechanism for Sc catalyzed alkylation of pyridines



1.2.5 Nickel Catalyzed C-H Activation

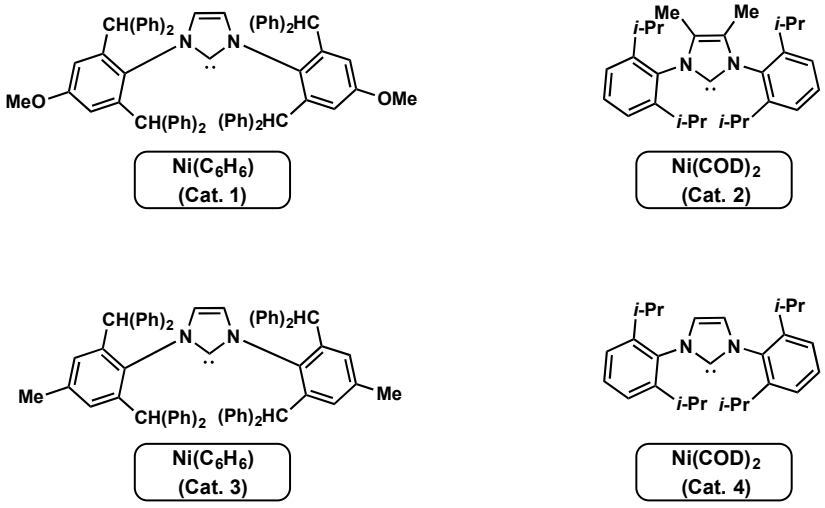
Hartwig and co-workers have reported that with the use of a nickel catalyst, one could hydroarylate electron deficient arenes to obtain linear alkyl arenes products using terminal alkenes.[19] The optimal catalyst that was used was $Ni(iPr)_2$ over $Ni(COD)_2$ to mitigate the formation of side products. A variety of acyclic and cyclic alkenes are tolerated with the optimal conditions mentioned in (**Table 1.7**). The use of simple terminal olefins provided good yields and great control for the linear product over the branch. Cyclic systems and functionalized terminal alkenes were also well tolerated in the reaction such as allylic amines, acetals and esters.

Table 1.7: Select examples of Ni catalyzed alkylation of electron deficient arenes with various α-olefins



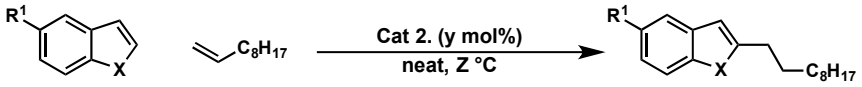
A year later Hartwig and co-workers developed another method of alkylation but now with a variety of heteroarenes: indoles, pyroles, benzofurans and furans.[20] The catalytic system depends on the use of a $Ni(COD)_2$ precatalyst along with sterically hindered and electron-rich *N*-heterocyclic carbene ligand. The use of the sterically hindered carbene ligand allowed for the favored anti-markovnikov products using α-olefins. The use of four different catalyst varying the identity of the NHC allowed the reaction to perform optimally depending on the heteroarene and alkene that was being reacted with one another (**Figure 1.5**).

Figure 1.5: Select examples of Ni NHC catalysts



The reactivity of indoles was very dependent on the substituent on the nitrogen. The smaller size substituent allowed for a higher yielding reaction and after testing substituent in size from methyl to isopropyl to TBDMS, it was determined that a methyl group was best suited. Hartwig and co-workers also noted that *N*-benzylindoles are also tolerated, but not as efficient compared to the *N*-methylindoles. Substitution at the 5 position of the indoles allowed for a variety of 5 substituted indoles to be tested from a fluoro or a methoxy groups. Carbonyl compounds at the 5 position such as an acyl and methyl ester group is tolerated which was furnished in good yields. Lastly, boronate esters were also a valid substituent where Hartwig and co-workers report a 45% yield, giving a very versatile product that could further be manipulated (**Table 1.8**). Benzofurans also underwent alkylation with terminal alkenes. Similar to the indoles, benzofurans tolerated a variety of substituents at the 5 position, similar to that of the indoles. One note is that the reaction with benzofurans were a lot more facile where catalyst loadings and the temperature were allowed to be lower.

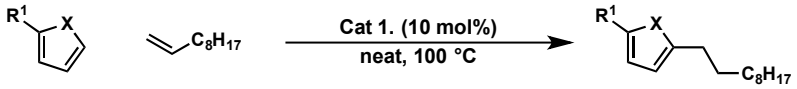
Table 1.8: Select examples of Ni catalyzed alkylation of benzoheteroarenes



Entry	X	R^1	Y (mol%)	Z (°C)	Yield (%)
1	O	OMe	2	50	94
2	O	F	2	50	99
3	NMe	CO_2Me	2	100	77
4	NMe	COMe	10	100	62
5	NMe	Bpin	10	100	45

Hartwig and co-workers also report that 5-memebered heterocycles such as *N*-methylpyrroles and furans are able to react with terminal alkenes as well (**Table 1.9**). Low yields for the simple *N*-methylpyrroles and furan is due to a mixture of mono- and di-alkylation at the C2 and C5 position. Other heteroarenes and substituents such as thiophenes and halogens were also tested but no product was obtained.

Table 1.9: Select examples of Ni catalyzed alkylation of heteroarenes



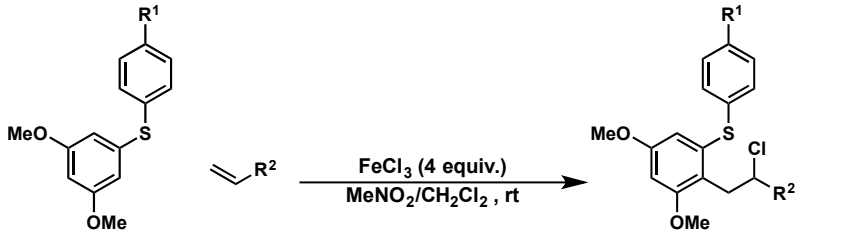
Entry	R^1	X	Yield (%)
1	H	O	38
2	Me	O	84
3	CO_2Me	O	58
4	COMe	O	68
5	$(CH_2)_2OCH$	O	64
6	H	NMe	33

1.2.6 Iron Catalyzed C-H Activation

Procter and co-workers report a sulfur directed iron mediated ortho alkylation of unactivated terminal alkenes.[21] This transformation uses an iron trichloride catalyst to provide linear β-chloroarenes. Simple and functionalized terminal alkenes baring halogens reacted, providing products in sufficient yields (**Table 1.10**).

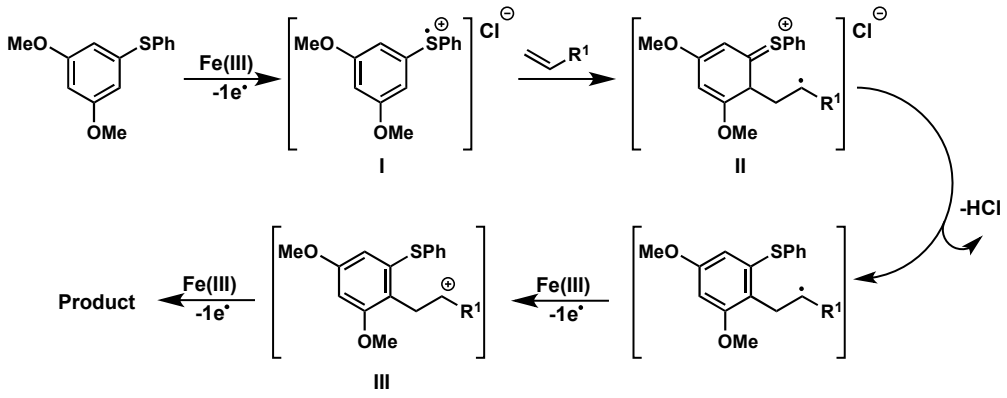
A possible mechanism for this reaction starts with a single electron transfer from the $FeCl_3$ which then gives the radical intermediate **I** which then reacts with the terminal alkene to form the sulfonium radical intermediate **II**. Deprotonation then occurs, giving off HCl, followed by oxidation with $FeCl_3$ giving carbocation **III** that is quenched by chloride and giving the final product (**Figure 1.6**).

Table 1.10: Select examples of Fe catalyzed sulfur directed alkylation



Entry	R^1	R^2	Yield (%)
1	H	C_6H_{13}	64
2	H	$C_6H_{12}Br$	60
3	H	$C_6H_{12}NO_2$	48
4	Br	C_6H_{13}	65
5	NO_2	C_6H_{13}	75

Figure 1.6: Plausible mechanism for Fe catalyzed sulfur directed alkylation

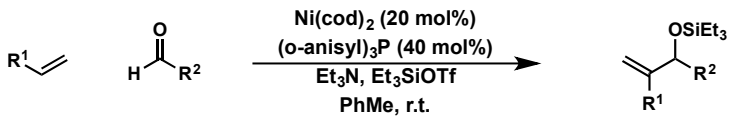


1.3 CARBONYL ADDITION

1.3.1 Nickel Catalyzed Carbonyl Addition

Jamison and Ng report the synthesis of protected allylic alcohols by using a nickel catalyst. [22] This 3-component intermolecular reaction uses an aldehyde, alpha olefin and silyl triflate. The reactions are operationally simple and can be conducted at room temperature and range from 2-8 hours. The reaction works with the simplest of α-olefins, ethylene gas at 1 atm (**Table 1.11**). An assortment of benzaldehydes are tolerated, from the simple parent benzaldehyde to electron-rich benzaldehydes and ortho-substituted benzaldehydes. Not being limited to only aryl aldehydes, alkyl aldehydes such as pivaldehyde and even functionalized alkyl aldehydes baring an ester for example is also tolerated and obtained in good yields. Other α-olefins such as 1-hexene is also tolerated but obtained in lower yields. It is also noted that the identity of the silyl group is not limited to just TES triflate, but others such as TMS and TBS were also useable.

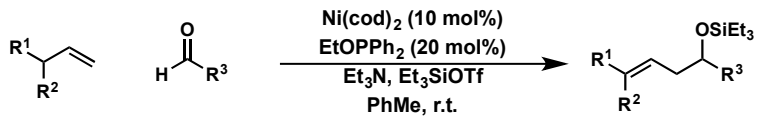
Table 1.11: Select examples of Ni catalyzed carbonyl addition using α-olefins

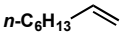
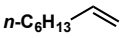
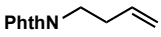


Entry	R^1	R^2	Yield (%)
1	H	Ph	82
2	H	*o*-Me-Ph	93
3	H	4-OMe-Ph	95
4	H	Piv	70
5	H	$(CH_3)_2CCO_2Me$	81
6	*n*-hexyl	Ph	48

To follow up with the coupling of simple alkenes to aldehydes, Jamison and co-workers now report a nickel catalyzed carbonyl-ene reaction using α-olefins and aryl aldehydes.[23] Jamison and co-workers note that by tuning the catalytic system found in their previous 3-component coupling of α-olefins, aldehydes and silyl triflates to obtain products of vinylation, by using diphenylethoxyphosphine ($EtOPPh_2$) now allows access to homoallylic silyl protected alcohols (**Table 1.12**). The product of propene gas and benzyl aldehyde was obtained in 73% yield. Products that could produce a mixture of *E* and *Z* isomers had the *E* isomer favored. The coupling of 1-octene for example was obtained in an 85% yield with a ratio of 75:25 favoring the *E* isomer. The use of electron rich aryl and alkyl aldehydes were also tolerated under the reaction conditions.

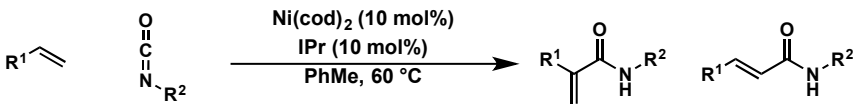
Table 1.12: Select examples of Ni catalyzed carbonyl-ene reaction with α-olefins



Entry	Alkene	R^2	*E:Z*	Yield (%)
1		Ph	n.a.	73
2		Ph	75:25	85 (95:5)
3		Piv	78:22	64 (>95:5)
4		Ph	95:5	86 (92:8)
5		4-OMe-Ph	83:17	76 (95:5)

Jamison and co-workers report the coupling of α-olefins to isocyanates using a nickel catalyst to form acrylamides.[24] Some of the pioneering working had been done by Hoberg who first reported the stoichiometric and catalytic coupling of phenyl isocyanate and ethylene gas, using a nickel catalyst.[25,26] Now with the use of catalytic amounts of $Ni(cod)_2$ and a NHC ligand, IPr the coupling of higher order α-olefins and alkyl substituted isocyanates can be performed (**Table 1.13**). The use of cyclic and acyclic substituted isocyanates was used and products were obtained in good yields. Simple and functionalized alkenes such as 1-octene, vinyl cyclohexane and allyl acetone were tolerated. In the cases where the yields are lower was due to the formation of the linear adduct rather than the major branched product. The formation of the observed branched coupling as opposed to the linear adduct can be explained where upon formation of the aza nickel cyclopentanone, the substituent of the alkene wants to be distal from the isopropyl group of the IPr ligand (**Figure 1.7**).

Table 1.13: Select examples of Ni catalyzed coupling of α-olefins with isocyanates



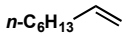
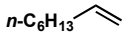
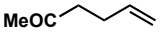
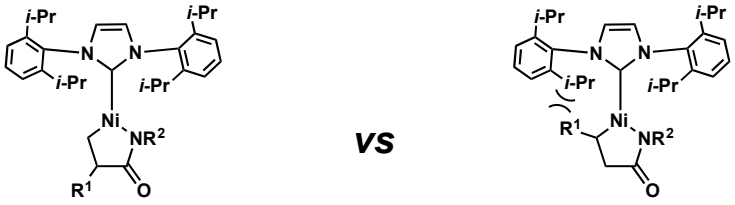
Entry	Alkene	R^2	Yield a:b (%)
1		*t*-Bu	74:17
2		Cy	79:14
3		*t*-Bu	91:0
4		Cy	74:5
5		*t*-Bu	70:2

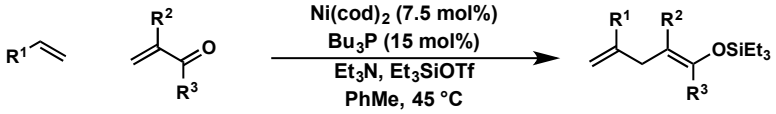
Figure 1.7: Rationale of regioselectivity for acrylamide products



In 2008 Jamison and co-workers report the conjugate addition of α-olefins to enones using a nickel catalyst.[27] By using $Ni(cod)_2$ as the nickel precatalyst and tributyl phosphine (other alkyl phosphines work as well), products of conjugate addition isolated as the enolsilane were obtained (**Table 1.14**). Unactivated olefins such as 1-octene and 2-hexylacroleain were tolerated in the reaction conditions and provided addition product. Ratios of *E* and *Z* isomers favored the *E* isomer and gave high regioselectivity. This control stems from R^2 and R^3 substituents being as far apart from each other as possible. A possible mechanism starts with the nickel metal, alkene and enone coming together to form the oxa-π-allyl nickel complex **II**. Next intermediate **II** reacts with the silyl source giving complex

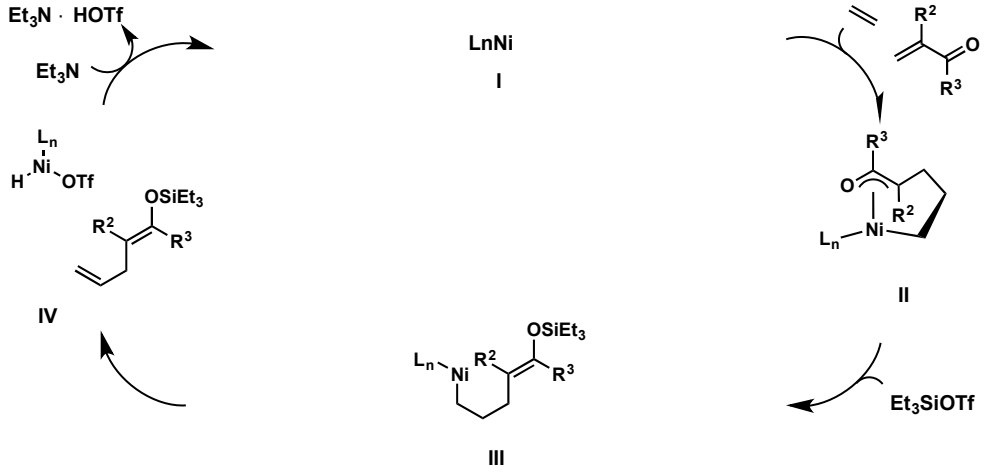
III that readily undergoes β-hydride elimination giving your desired product and the nickel hydride species which further reacts with trimethylamine then closing the catalytic cycle and regenerating the nickel (0) (**Figure 1.8**).

Table 1.14: Select examples of Ni catalyzed conjugate addition with α-olefins



Entry	R^1	R^2	R^3	*E:Z*	Yield (%)
1	H	Me	H	95:5	52
2	H	Me	Ph	95:5	90
3	H	Me	*p*-anisyl	91:9	94
4	H	*n*-Bu	2-furyl	75:25	95
5	*n*-hexyl	*n*-hexyl	H	95:5	67

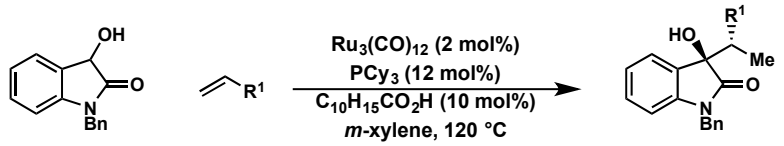
Figure 1.8: Plausible mechanism for Ni catalyzed conjugate addition of enones

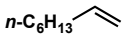
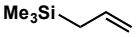


1.3.2 Ruthenium Catalyzed Carbonyl Addition

Krische and co-workers report the addition of α-olefins to *N*-benzyl-3-hydroxyoxindoles with the use of a ruthenium catalyst.[28] The products obtained are regio- and diastereoselective (**Table 1.15**). Simple α-olefins such as ethylene gas can be used to couple and obtain products of carbonyl addition. More functionalized α-olefins such as allylsilane is also tolerated and was obtained in a 95% yield and >20:1 diastereoselectivity in favor of the *anti*-diastereomer. It is noted by the authors that the use of a catalytic amount of an acid co-catalyst was required to have the reaction run efficiently and provide excellent yields.

Table 1.15: Select examples of Ru catalyzed hydrohydroxyalkylation



Entry	Alkene	d.r.	Yield (%)
1		n.a.	89
2		n.a.	90
3		>20:1	83
4		>20:1	95
5		>20:1	94

1.3.3 Osmium Catalyzed Carbonyl Addition

Krische and co-workers report the addition of α-olefins to hydroxy esters, α-ketols and diols with the use of a osmium catalyst.[29] In contrast to the work previously reported by Krische using ruthenium, the use of a osmium metal was key in being able to access other

coupling partners with α-olefins.[28] Ethyl mandelates electron rich or poor were tolerated, as well as heterocyclic hydroxy esters (**Table 1.16**). Higher order α-olefins such as 1-octene also provide products of carbonyl addition, giving the *syn*-diastereomer and in a usable 4:1 ratio. Coupling of α-olefins with the osmium system was also applicable to α-ketols and 1,2-diols in good yields (**Table 1.17** and **1.18**). The use of an acid-co-catalyst was used in the case of coupling with diols to increase conversion.

Table 1.16: Select examples of Os catalyzed hydrohydroxyalkylation of hydroxy esters

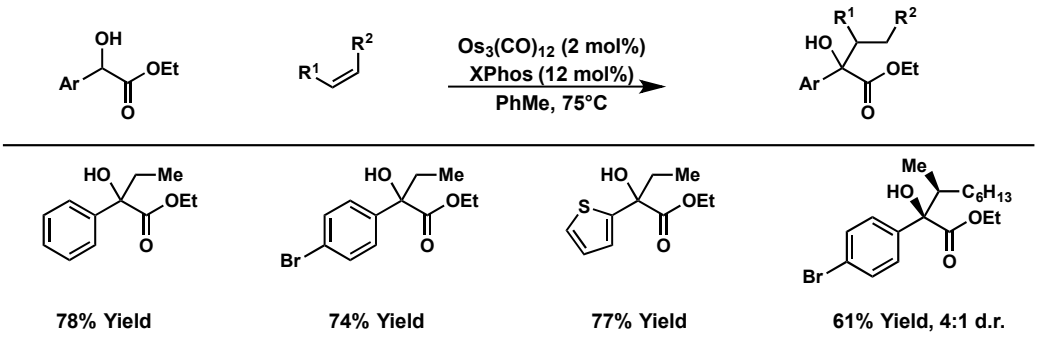


Table 1.17: Select examples of Os catalyzed hydrohydroxyalkylation of α-ketols

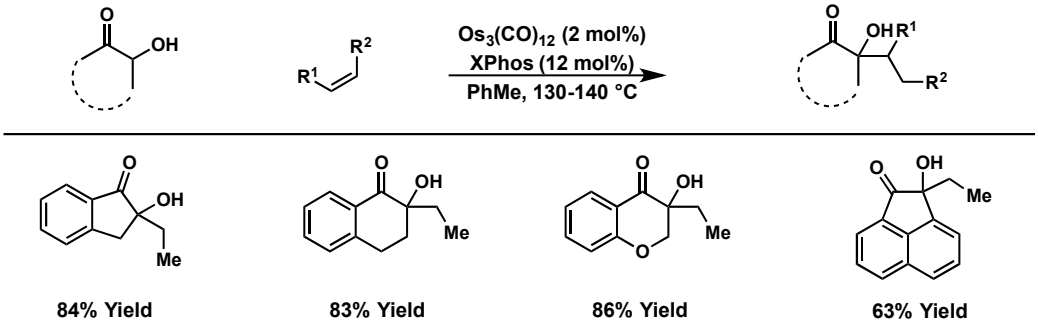
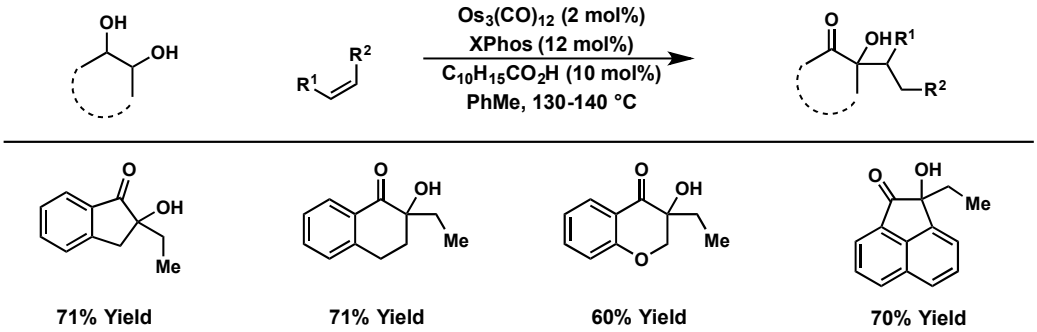


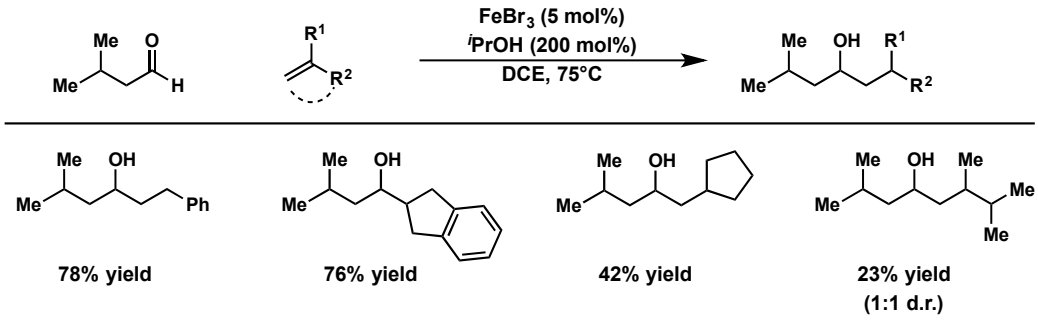
Table 1.18: Select examples of Os catalyzed hydrohydroxyalkylation of 1,2-diols



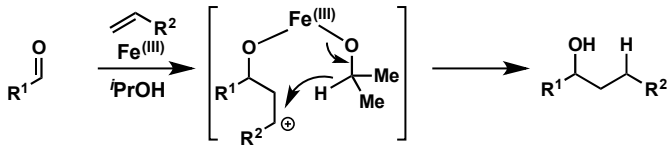
1.3.4 Iron Catalyzed Carbonyl Addition

Ye and co-workers report the addition of simple alkenes to unactivated aldehydes with the use of an iron catalyst.[30] The reaction uses iron tribromide with isopropanol and can couple a variety of aryl and alkyl aldehydes with aryl and alkyl alkenes (**Table 1.19**). To focus on the addition of α-olefins, the reaction developed by Ye and co-workers unfortunately was not as efficient. The low yields with the highest being 42% yield with methylenecyclopentane and 23% yield with 2,3-dimethyl-1-butene giving a 1:1 mixture of diastereomers. A possible rationale as to why the simple α-olefins are not as efficient lies in the proposed mechanism (**Scheme 1.4**). The resulting carbocation that is formed from the Meerwein-Pondorf-Verley like mechanism would not be as stabilized from the alkyl groups compared to the aryl substituents. Another proposed mechanism presented by Ye and co-workers induce a 1,5-H shift, that has been previously reported in combination with the results from Ye that the use of Bronsted acids also facilitates the reaction (**Scheme 1.5**).[31,32]

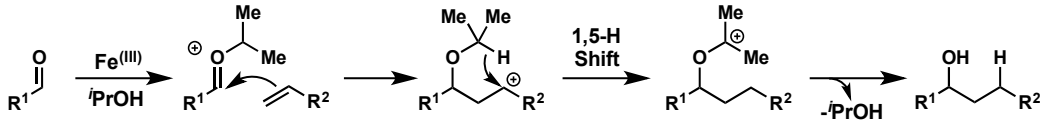
Table 1.19: Select examples of Fe catalyzed carbonyl addition



Scheme 1.4: Plausible MVP mechanism for Fe catalyzed carbonyl addition



Scheme 1.5: Plausible 1,5-H Shift mechanism for Fe catalyzed carbonyl addition



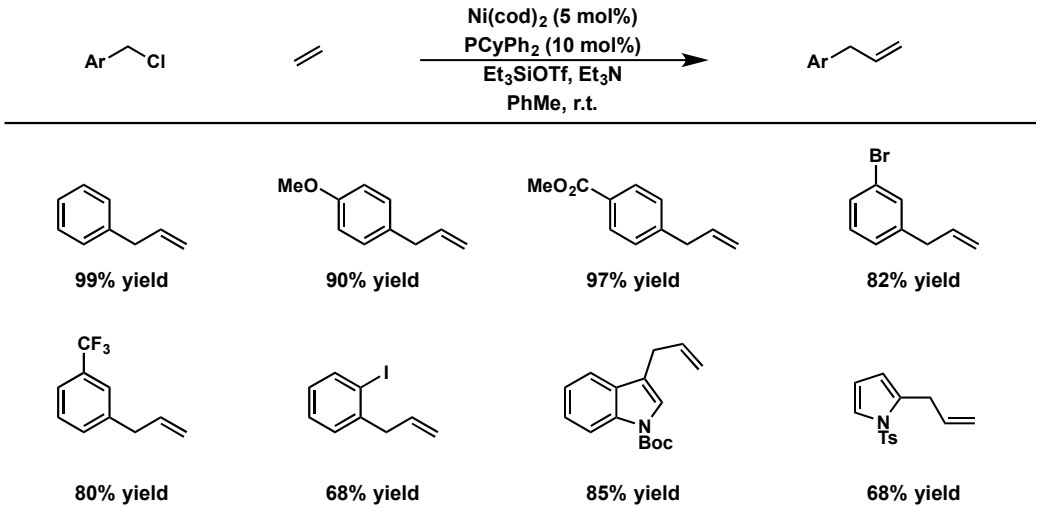
1.4 CROSS COUPLING

1.4.1 Nickel Catalyzed Cross Coupling

In 2011 Jamison and co-workers report a nickel-catalyzed benzylation of simple alkenes to provide allylbenzene products.[33] This work reported by Jamison and co-workers address the problem of expanding the scope of coupling to benzyl halides to other olefins that do not bear substituents to facilitate coupling such as acrylates, styrenes or *N*-vinyl amides. By using a monodentate phosphine modified nickel catalyst at room temperature

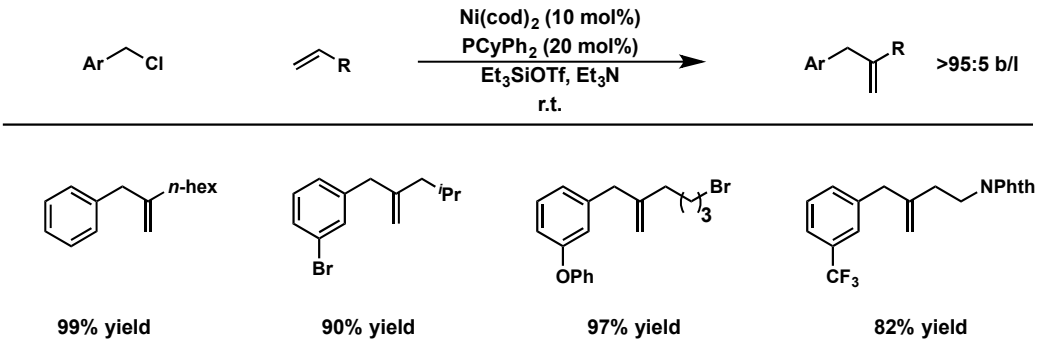
Jamison and co-workers are able to obtain the allylbenzene product from the coupling of benzyl chloride and ethylene gas in nearly quantitative yield (**Table 1.20**). Substituents at the para, meta and ortho position are tolerated within the reaction conditions with a wide range of electron donating and withdrawing groups such as methoxy, methyl ester, halides and trifluoromethyl groups. Not being limited to only aryl chlorides, heterocyclic groups were also tolerated such as indoles and pyroles providing the corresponding allyl products in good yield.

Table 1.20: Select examples of Ni catalyzed cross-coupling using benzyl chlorides and ethylene gas



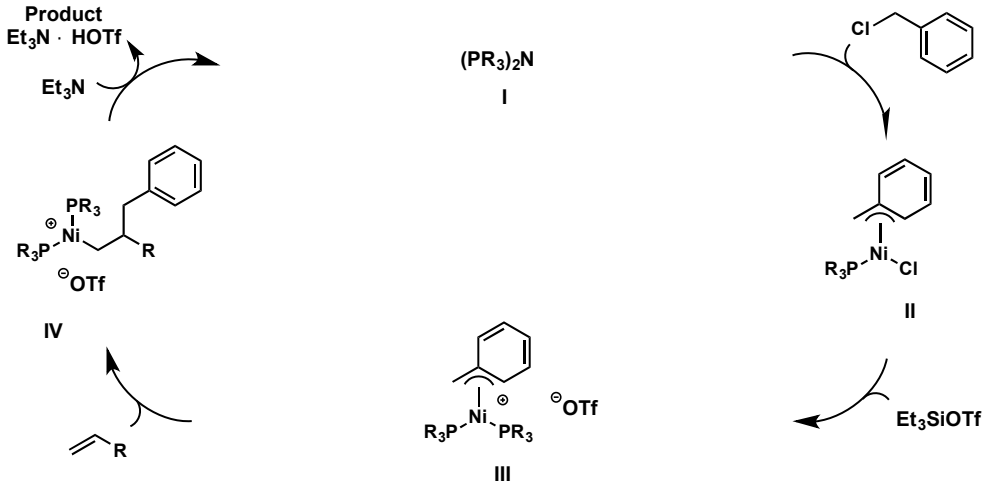
To further test the scope of the reaction, other simple α-olefins and simple alkenes were tolerated with the reaction conditions (**Table 1.21**). The reaction provided the branched products in good yields. Simple alkyl, halo and phthalimide functional groups were also tolerated in the higher order alkenes, providing a useful functional handle for further synthetic transformations.

Table 1.21: Select examples of Ni catalyzed cross-coupling using benzyl chlorides and higher order alkenes



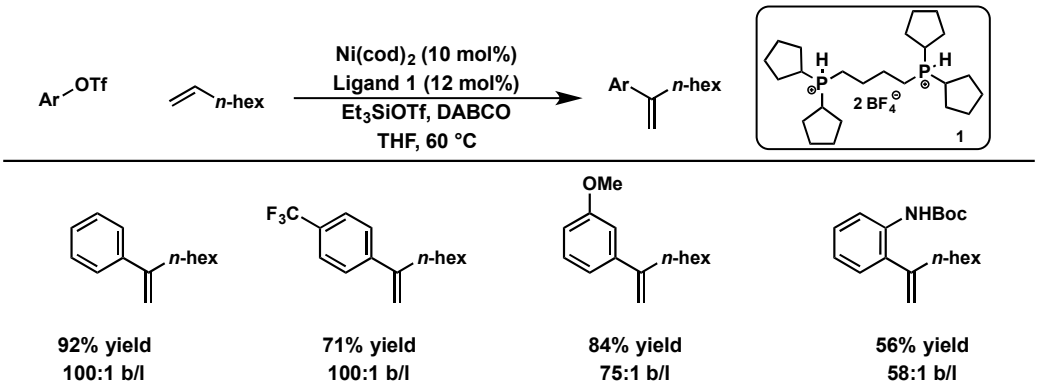
A plausible mechanism for the transformation presented by Jamison and co-workers start with the nickel complex oxidatively adding into the benzyl chloride providing a nickel complex with a η^3- benzyl ligand **II** (**Figure 1.9**). The authors provide an X-ray crystal structure as proof of nickel complex **II**. Counteranion exchange then occurs with the Et_3SiOTf to provide a cationic nickel complex **III** followed by a migratory insertion into the olefin **IV**. The nickel is placed distal from the aryl group which then undergoes a β-hydride elimination to provide the allylbenzene product and triethylamine regenerates the nickel catalyst **I**.

Figure 1.9: Plausible Ni catalyzed benzylation using benzyl chlorides



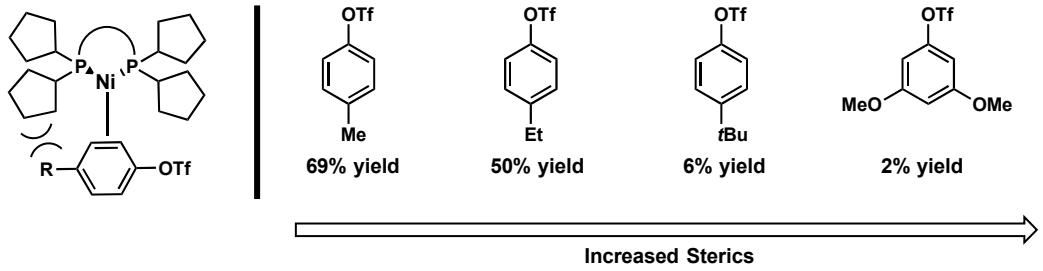
In 2014 Jamison and co-workers published the coupling aryl sulfonates with simple alkenes, selective for the branched products.[34] By using a cationic nickel system with a bidentate phosphine ligand desired branched coupling products of aryl triflates were obtained (**Table 1.22**). Substituents at all positons on the phenyl ring are tolerated and covered electron donating and withdrawing groups.

Table 1.22: Select examples of Ni catalyzed cross-coupling using aryl sulfonates and 1-octene



Further mechanistic studies conducted by Jamison and co-workers found that the size of substituent para from the *ortho*-triflate has a direct impact in efficiency and time of the described coupling reaction of aryl triflates. This is because the coordination of the aryl group with the nickel complex has a disfavorable interaction with the cyclopentyl group of the bidentate phosphine ligand. As the size of the alkyl group increases from methyl to *tert*-butyl the yields drop to trace amounts of product (**Figure 1.10**). It was also noted that the use of di-*meta* substituted aryl systems also did not provide any coupling product due to the sterics of the whole system, lacking an optimal point of coordination.

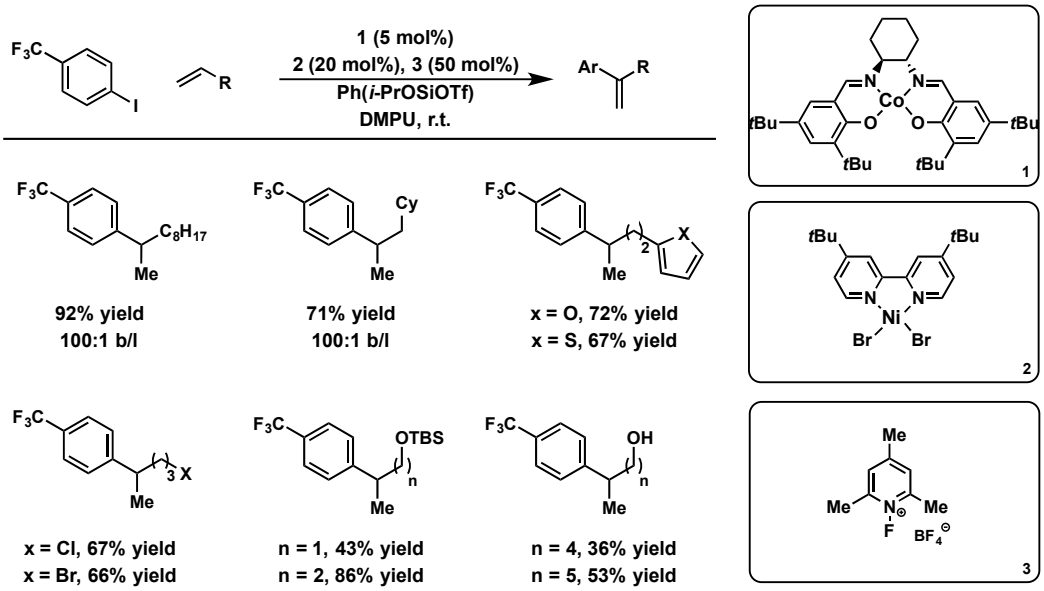
Figure 1.10: Steric effects on Ni catalyzed cross-coupling of aryl sulfonates



In 2016 Shenvi and co-workers report a branch selective hydroarylation of iodoarenes with alkenes.[35] The use of a cobalt salen, nickel precatalyst and pyridinium salt allowed for the hydrogen atom transfer (HAT) reaction from a metal hydride and alkene to cross couple with iodoarenes (**Table 1.23**). A wide variety of alkenes were tolerated in the mild reaction conditions providing the branched coupling products. Cycloalkyl, heteroaryl and halo substituted alkenes were applicable to the reaction conditions. Free alcohols and silyl protected alcohols were also able to couple with the described reaction conditions. Not being limited to only 4-trifluoromethyl iodophenyl as the coupling partner, but other

iodoarenes baring electron-donating and withdrawing such as methoxy and cyano groups were also tolerated.

Table 1.23: Select examples of Ni catalyzed HAT using iodoarenes and alkenes

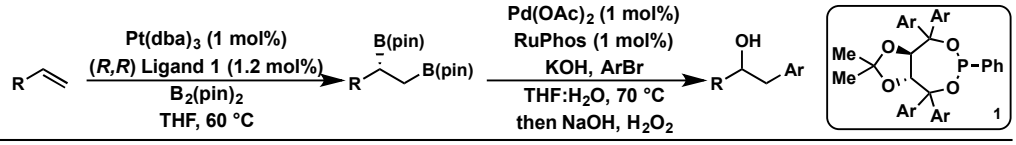


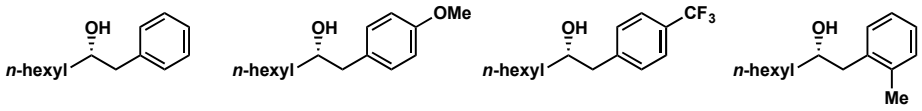
1.4.2 Platinum and Palladium Catalyzed Cross Coupling

In 2014 Morken and co-workers report an enantioselective diboration of terminal alkenes followed by a palladium cross-coupling with aryl halides and alkyl halides compounds.[36] The first step in the synthesis of chiral alpha aryl secondary alcohols is the diboration using pinacolborane and platinum metal with a TADDOL based phosphine ligand followed by a Suzuki coupling reaction, all done in one pot (**Table 1.24**). Electron rich and electron poor arenes were well tolerated in the reaction, as well as heteroaromatics such as furans and pyridines. With the use of aryl alkanes instead of aryl halides the synthesis of chiral homoallylic alcohols could also be achieved, providing a versatile motif that can be further used in organic chemistry (**Table 1.25**). The stereochemistry of the olefin is retained

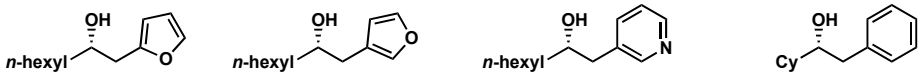
during the Suzuki, thus providing an efficient way in accessing configurationally defined disubstituted alkenes.

Table 1.24: Select examples of Pt/Pd catalyzed cross coupling using alkenes and aryl halides



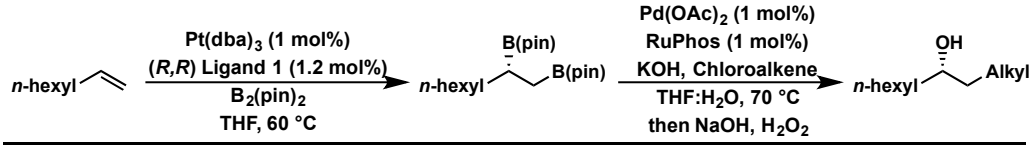


96% yield, 97% ee | 91% yield, 97% ee | 85% yield, 97% ee | 80% yield, 94% ee



79% yield, 96% ee | 63% yield, 96% ee | 86% yield, 97% ee | 93% yield, 99% ee

Table 1.25: Select examples of Pt/Pd catalyzed cross coupling using alkenes and alkyl halides



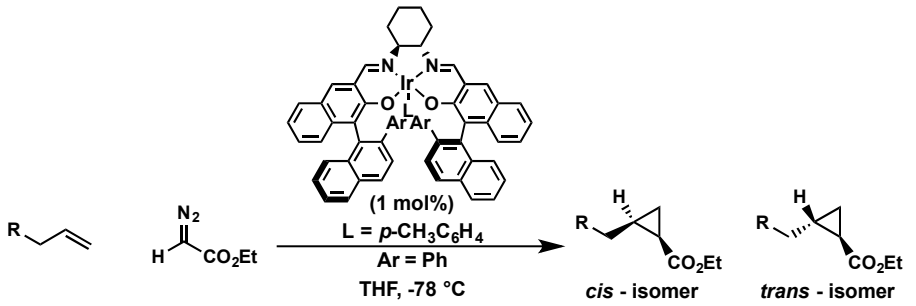
89% yield, 97% ee | 92% yield, 97% ee | 90% yield, 97% ee | 83% yield, 96% ee

1.5 CYCLOPROPANATION

1.5.1 Iridium Catalyzed Cyclopropanation

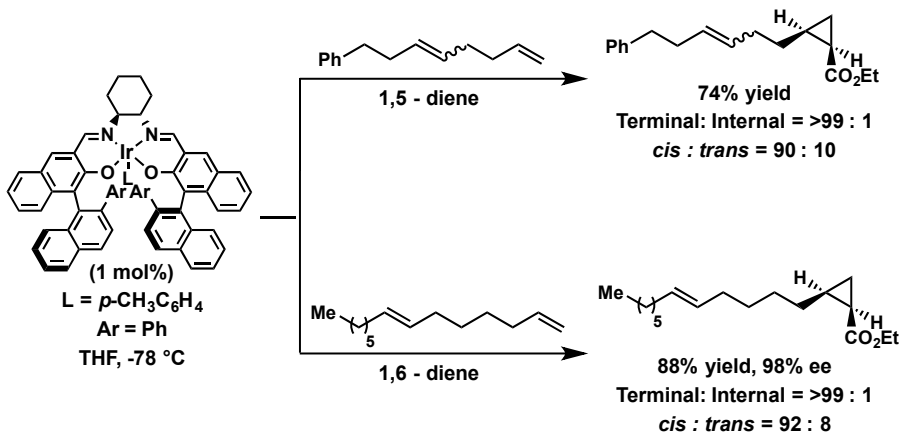
Katsuki and co-workers report a enantio- and *cis*- selective cyclopropanation of alkenes. The reaction uses an iridium salen complex and display great selectivity for the *cis*-isomer in good yields and excellent enantioselectivity (**Table 1.26**). Simple aliphatic alkyl and cyclic alkyl groups performed. Benzoyl groups were also able to perform under the reaction conditions, although the preferences for *cis* wasn't as profound compared to the other substrates. This method was also applicable to 1,5 and 1,6 dienes providing cyclopropanated product in good yields, and displayed high preference for the terminal olefin over the internal olefin (**Scheme 1.6**).

Table 1.26: Select examples of Ir salen catalyzed cyclopropanation with alkenes



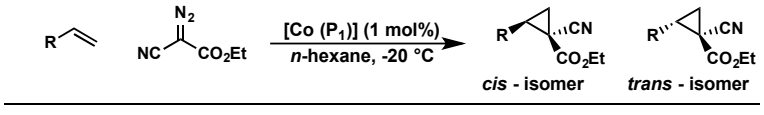
Entry	R	ee (%)	*cis : trans*	Yield (%)
1	n-C_6H_{13}	98	98 : 2	62
2	$BnOC_4H_8$	97	95 : 5	95
3	Cy	98	96 : 4	46
4	PhC_2H_4	96	96 : 4	93
5	BzO	92	86 : 14	83

Scheme 1.6: Cyclopropanation of 1,5 and 1,6 dienes

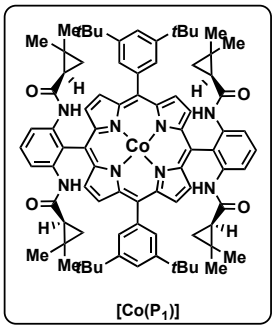


In 2010 Zhang and co-workers report a highly stereoselective cyclopropanation of alkenes with α-cyanodiazoacetates. Zhang and co-workers described a cobalt porphyrin catalyst that allowed the reaction to occur in good yields (**Table 1.27**).

Table 1.27: Select examples of Ir salen catalyzed cyclopropanation with alkenes



Entry	R	ee (%)	*cis : trans*	Yield (%)
1	n-C_4H_9	96	99 : 1	86
2	n-C_6H_{13}	92	99 : 1	72
3	$MeCO_2$	71	99 : 1	97
4	PhC_2H_4	91	99 : 1	90



1.6 CONCLUSION

The transformation of simple linear α-olefins to value added products still remains an active research field. Significant efforts have been put forth to utilize a variety of simple α-olefins such as ethylene gas and others. A variety of transition metals has displayed their

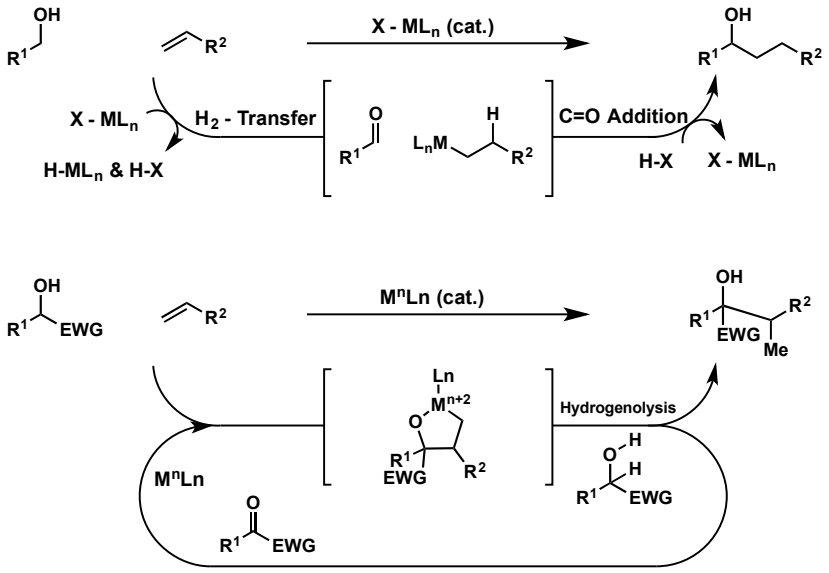
capability to convert simple α-olefins to value added products. The future of being able to convert α-olefins to other value added products may be hidden with transition metals.

Chapter 2: Ruthenium Catalyzed C-C Coupling of α-Olefins and Styrenes to 3-Hydroxy-2-Oxindoles

2.1 INTRODUCTION

α-Olefins are the most abundant chemical feedstocks with the exception of alkanes and their use can be seen in the synthesis of many diverse chemical products.[1,37] With the exception of hydroformylation, intermolecular catalytic reductive C-C couplings of α-olefins to carbonyl compounds are limited to non-existent.[4,22] To address this issue the Krische group has discovered a variety of hydrogen-mediated reductive couplings beyond hydroformylation, where π- unsaturated reagents are hydrogenated to form new C-C bonds.[38,39] These transformations discovered by the Krische group typically proceed by way of metallacycle formation followed by hydrogenolysis (**Figure 2.1**, top). In recent discovery, the Krische group has discovered another pathway involving alcohol-mediated transfer hydrogenolysis of metallacycles in the couplings of dienes to α-hydroxy esters or *N*-benzyl-3-hydroxy-2-oxindoles (**Figure 2.1**, bottom).[28,29]

Figure 2.1: Catalytic mechanisms *via* hydrogenation or transfer hydrogenation

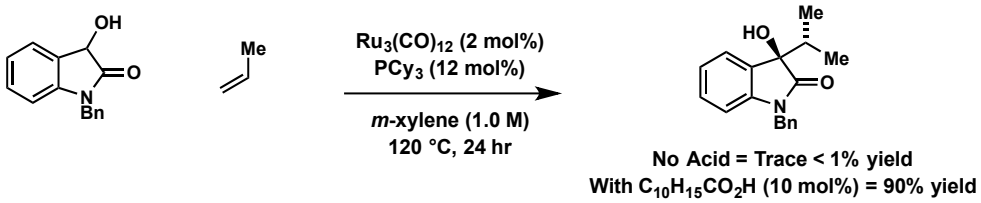


2.2 Background and Reaction Development

With the discovery of an alcohol-mediated transfer hydrogenolysis of metallacycle intermediates, the Krische group was prompted to investigate the possibility of using α-olefins as the π-unsaturate in promoting the formation of new C-C bonds. Based on prior work with similar reactive modes, *N*-benzyl-3-hydroxy-2-oxindoles was the coupling partner of choice. In an initial experiment the use of *N*-benzyl-3-hydroxy-2-oxindole was exposed to ethylene gas using previously establish conditions.[40] The initial experiment provided the product of hydrohydroxyalkylation in 20% yield. In the case of a mono-substituted α-olefins such as propylene gas, only trace amounts of coupling product were observed as the isopropyl-substituted oxindole. These initial results suggest that the carbonyl-alkene oxidative coupling was operative, but inefficient with the current reaction conditions. This lack of efficiency lead to the optimization of the previously establish conditions used in the coupling of dienes to *N*-benzyl-3-hydroxy-2-oxindole.[40] It was previously shown that the use

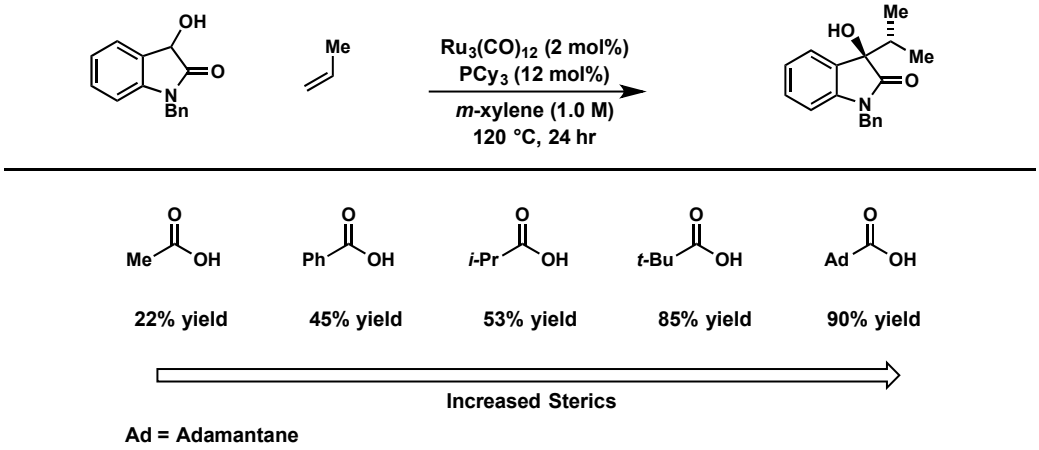
carboxylic acid co-catalyzes the cleavage of oxametallacycles to improve rate and conversion.[41] A variety of carboxylic acids were screened and was found that the use of 1-adamantanecarboxylic acid provided the desired coupling of product between propylene and *N*-benzyl-3-hydroxy-2-oxindole in 90% yield as a single regioisomer (**Scheme 2.1**).

Scheme 2.1: Effect of acid co-catalyst between *N*-benzyl-3-hydroxy-2-oxindole and propylene



Compared to the other carboxylic acids screened it seemed that the use of more bulky acids had a positive effect on the reaction (**Figure 2.2**). It is to be noted that the use of non-carboxylic acids had no effect in improving the reaction.

Figure 2.2: Screen of different acid co-catalysts



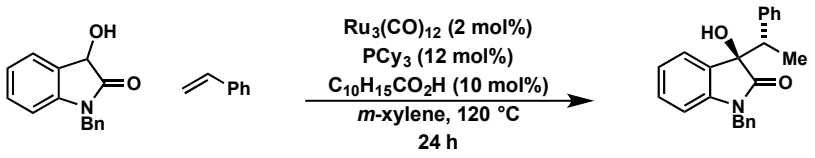
This could be interpreted by a possible 6-membered transition state in helping facilitate the cleavage of the oxaruthenacycle with the addition of the carboxylic acid co-

catalyst. This is in contrast to a 4-membered transition state without the addition of a carboxylic acid co-catalyst, but rather with another molecule of the starting material alcohol (**Figure 2.3**).

Figure 2.3: Possible cleavage transition states of the oxaruthenacycle

To our delight the use of styrene was also compatible with our reaction conditions, thus prompted us to probe the optimal amount of alkene to use in excess (**Table 2.1**). It was found that 400 mol% was optimal and provided the desired coupling product in 94% yield as a single regio- and diastereomer.

Table 2.1: Optimization for amount of styrene

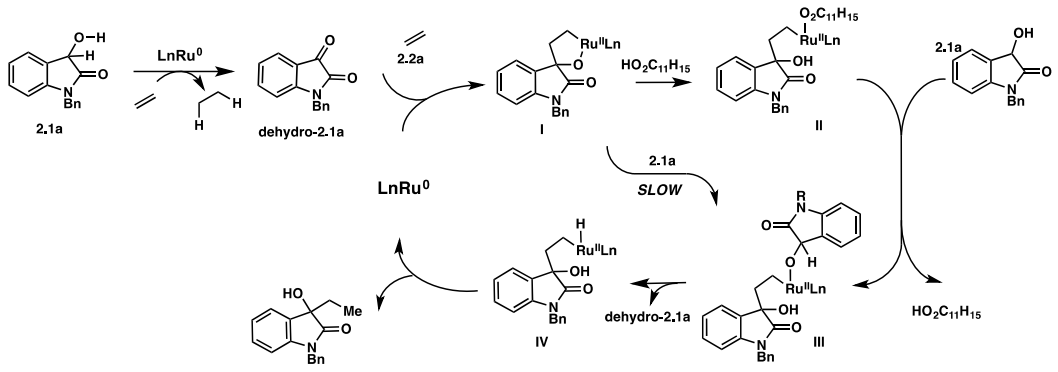


Entry	Styrene (mol%)	Yield (%)
1	100	57
2	200	69
3	300	79
4	400	94

2.3 PROPOSED MECHANISM

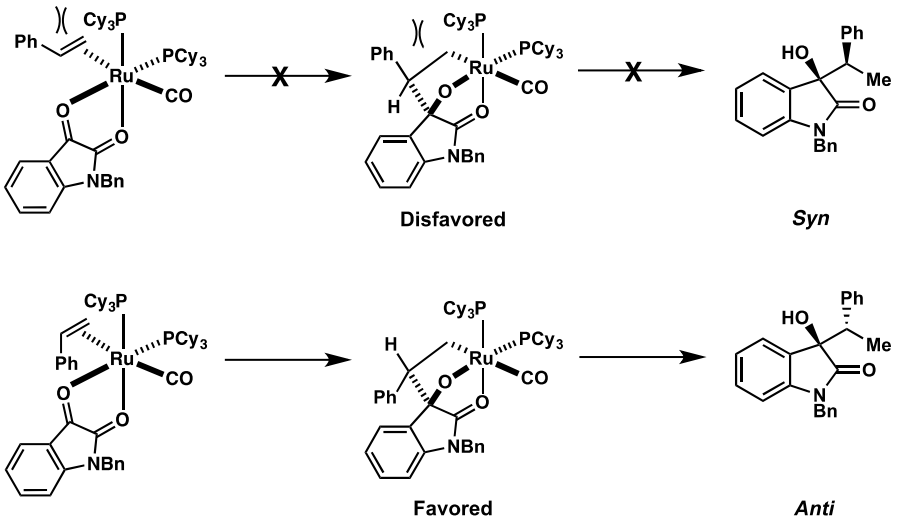
A plausible mechanism to account for such transformation begins with the discrete formation of a monometallic ruthenium (0) complex from $Ru_3(CO)_{12}$ and PCy_3 (**Figure 2.4**). The first *N*-benzyl-3-hydroxy-2-oxindole **2.1a** is dehydrogenated to obtain the *N*-benzyl protected isatin **dehydro-2.1a**, which then undergoes oxidative coupling with ethylene gas to form the oxaruthenacycle **I**. Upon formation of the oxaruthenacycle, the metallacycle has two possible paths, first being the direct cleavage from another molecule of the *N*-benzyl-3-hydroxy-2-oxindole. This pathway may be prohibitively slow to convert the oxaruthenacycle **I** to the ruthenium alkoxide **III**. This once again maybe explain by the cleavage of the oxaruthenacycle by a 4-membered transition-state. A possibly more favorable pathway is the cleavage of the oxaruthenacycle **I** by protonolysis with the 1-adamantanecarboxylic acid via a 6-membered transition state. This protonolysis would then furnish ruthenium alkoxide **II** followed by a alkoxide exchange with another molecule of *N*-benzyl-3-hydroxy-2-oxindole furnishing alkoxide **III**. Now with alkoxide **III** a β-hydride elimination can then occur and expel another molecule of isatin to re-enter the catalytic cycle and also provide the ruthenium hydride **IV**. Upon C-H reductive elimination furnishes the product of hydrohydroxyalkylation and regenerating the ruthenium (0) catalyst, closing the catalytic cycle.

Figure 2.4: Proposed catalytic mechanism for *N*-benzyl-3-hydroxy-2-oxindole and ethylene



A possible explanation for the observed *anti*-diastereomer stems from the trajectory of the alkene to form the oxaruthenacycle (**Figure 2.5**). In the top reaction, the phenyl ring of the styrene could have an unfavorable steric interaction with a cyclohexyl ring upon formation of the oxaruthenacycle, which would in turn form the *syn*-diastereomer. In the bottom reaction, the phenyl ring of the styrene now avoids the steric interaction between the cyclohexyl ring of the tricyclohexylphosphine, thus eventually leading to the formation of the observed *anti* product.

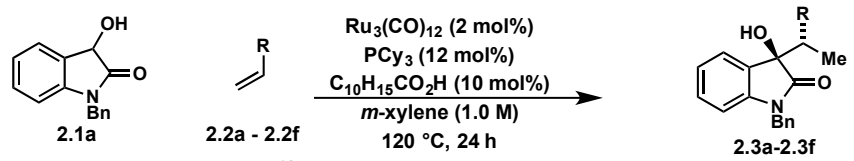
Figure 2.5: Proposed stereochemical model for observed *anti*-diastereomer between styrene and *N*-benzyl-3-hydroxy-2-oxindole



2.4 REACTION SCOPE

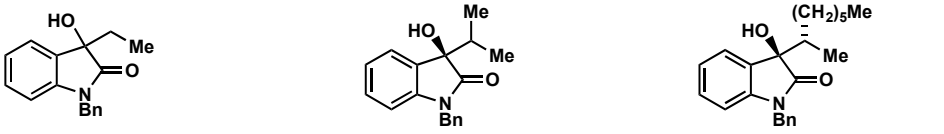
With the optimized reaction conditions in hand, the conditions were applied in the coupling of *N*-benzyl-3-hydroxy-2-oxindole to a variety of α-olefins (**Table 2.2**) The corresponding coupling products were obtained in excellent yields and with complete regioselectivity for the branched products. The assignment of the relative stereochemistry was corroborated by single X-ray diffraction of **2.3c**. Functional group compatibility is displayed with products **2.3d** and **2.3e** which incorporate alkoxy and silyl groups at the allylic position. It is also noteworthy that the coupling product with allylbenzene **2.3f** proceed smoothly, with no olefin isomerization which is known with $Ru_3(CO)_{12}$ derived catalysts.[42,43] Some limitations of this work were that the use of 1,2-disubstituted olefins did not work with the optimized reaction conditions.

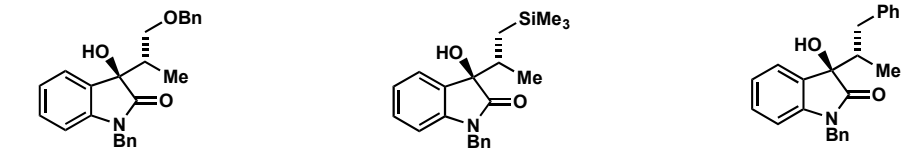
Table 2.2: Coupling of α-olefins to *N*-benzyl-3-hydroxy-2-oxindoles



R = H, 2.2a | R = Me, 2.2b | R = C_6H_{13}, 2.2c

R = CH_2OBn, 2.2d | R = CH_2SiMe_3, 2.2e | R = CH_2Ph, 2.2f



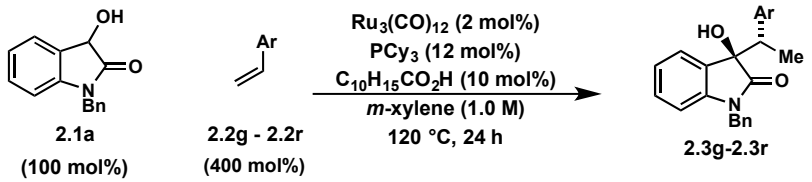


Substituted styrenes were also compatible with our optimized reaction conditions that provided coupling products in good yields, good selectivity for the branched coupling products and excellent selectivity of the *anti*-diastereomer (**Table 2.3**). Based on X-Ray diffraction analysis, the observed *anti*-diastereomer was the major diastereomer and corroborates with our proposed stereochemical model. Coupling of styrene derivatives proceed smoothly giving complete regioselectivity for the branched product with the exception for the 2-methoxy substituted styrene **2.3k**. A possible explanation for the decreased selectivity for the branched product could be due to sterics of the nearby methoxy group to the reactive site. Erosion of selectivity for the branched product can also be viewed with electron deficient styrene derivatives, due to a background reaction involving classical

conjugate addition. Lastly, heteroaromatics were also tolerated under the reaction conditions as shown with the 2-thienyl subsisted olefin **2.2r**.

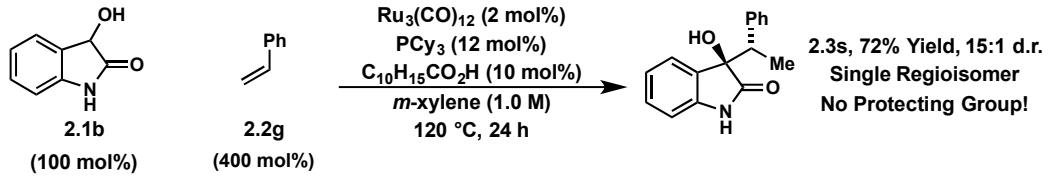
Non-protected 3-hydroxy-2-oxindoles were also tolerated with the described reaction conditions, providing the coupling product with styrene in 72% yield **2.3s** in excellent diastereoselectivity and exclusively the branched product (**Scheme 2.2**).

Table 2.3: Coupling of styrene derivatives with *N*-benzyl-3-hydroxy-2-oxindoles



Entry	Ar Moiety	Product	b/l	Yield [%] (d.r.)
1	Ph, 2.2g	2.3g	> 20 : 1	94 (> 20 : 1)
2	2-napthyl, 2.2h	2.3h	13 : 1	81 (> 20 : 1)
3	4-MeC_6H_4, 2.2i	2.3i	> 20 : 1	83 (> 20 : 1)
4	4-$MeOC_6H_4$,, 2.2j	2.3j	> 20 : 1	77 (> 20 : 1)
5	2-$MeOC_6H_4$, 2.2k	2.3k	1.3 : 1	91 (> 20 : 1)
6	4-$Me_2NC_6H_4$, 2.2l	2.3l	> 20 : 1	65 (> 20 : 1)
7	1,3-benzodioxole, 2.2m	2.3m	> 20 : 1	81 (> 20 : 1)
8	4-ClC_6H_4, 2.2n	2.3n	> 20 : 1	82 (> 20 : 1)
9	4-$CF_3C_6H_4$, 2.2o	2.3o	> 20 : 1	81 (> 20 : 1)
10	4-CNC_6H_4, 2.2p	2.3p	8.5 : 1	76 (> 20 : 1)
11	4-$CO_2MeC_6H_4$, 2.2q	2.3q	4 : 1	87 (> 20 : 1)
12	2-thienyl, 2.2r	2.3r	> 20 : 1	87 (> 20 : 1)

Scheme 2.2: Coupling of styrene with 3-hydroxy-2-oxindole



2.5 CONCLUSION

In summary, as described are the first examples of metal catalyzed hydrohydroxyalkylation of α-olefins and styrene derivatives to *N*-benzyl-3-hydroxy-2-oxindole. This process was enabled by a new mechanistic pathway discovered in the Krische group by way of carbonyl-olefin oxidative coupling which undergo transfer hydrogenolysis by alcohol reactant to furnish the product of hydrohydroxyalkylation. Further studies will be directed towards the development of related catalysts to enable the coupling of α-olefins with other electrophiles such as aliphatic alcohols in the absence of stoichiometric metal-byproducts.

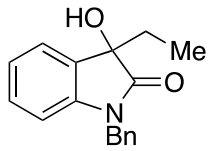
2.6 EXPERIMENTAL SECTION

General Information: All reactions were run under an atmosphere of argon. *m*-Xylene was distilled immediately before each use. Anhydrous solvents were transferred by oven-dried syringe. Sealed tubes (13×100 mm^2) were purchased from Fisher Scientific (catalog number 14-959-35C) and were dried in an oven overnight and cooled under a stream of argon prior to use. $Ru_3(CO)_{12}$ and PCy_3 were used as received from commercial suppliers. 1-Benzyl-3-hydroxy-2-oxindole **2.1a**, 3-hydroxy-2-oxindole **2.1b**, allyl benzyl ether **2.2d**, styrenes **2.2h**, **2.2l**, **2.2m** and **2.2o-2.2r** were prepared in accordance with literature procedures.[44–49] Preparative column chromatography employing silica gel was performed according to the

method of Still.[6] Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Adsorbents F_{254}). Visualization was accomplished with UV light followed by dipping in a p-anisaldehyde solution or magic stain and heating. Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 μm).

Spectroscopy and Spectrometry: Infrared spectra were recorded on a Thermo Nicolet 380 spectrometer. Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M or M+Na) or a suitable fragment ion. ^{1}H NMR spectra were recorded on a Varian Gemini (400 MHz) spectrometer at ambient temperature unless otherwise noted. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from trimethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuteriochloroform. Data are reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Varian Gemini (100 MHz) spectrometer and were routinely run with broadband decoupling. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm).

1-Benzyl-3-ethyl-3-hydroxyindolin-2-one (2.3a)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with ethylene. *m*-Xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) was added and the reaction was purged again with ethylene. The mixture was heated to 120 °C (oil bath temperature) for 24 h under an atmosphere of ethylene, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole. Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3a**) (71 mg, 0.27 mmol, 89%) as a colorless solid.

TLC (SiO_2): R_f = 0.45 (hexanes:ethyl acetate = 1:1).

m.p.: 123-125ºC

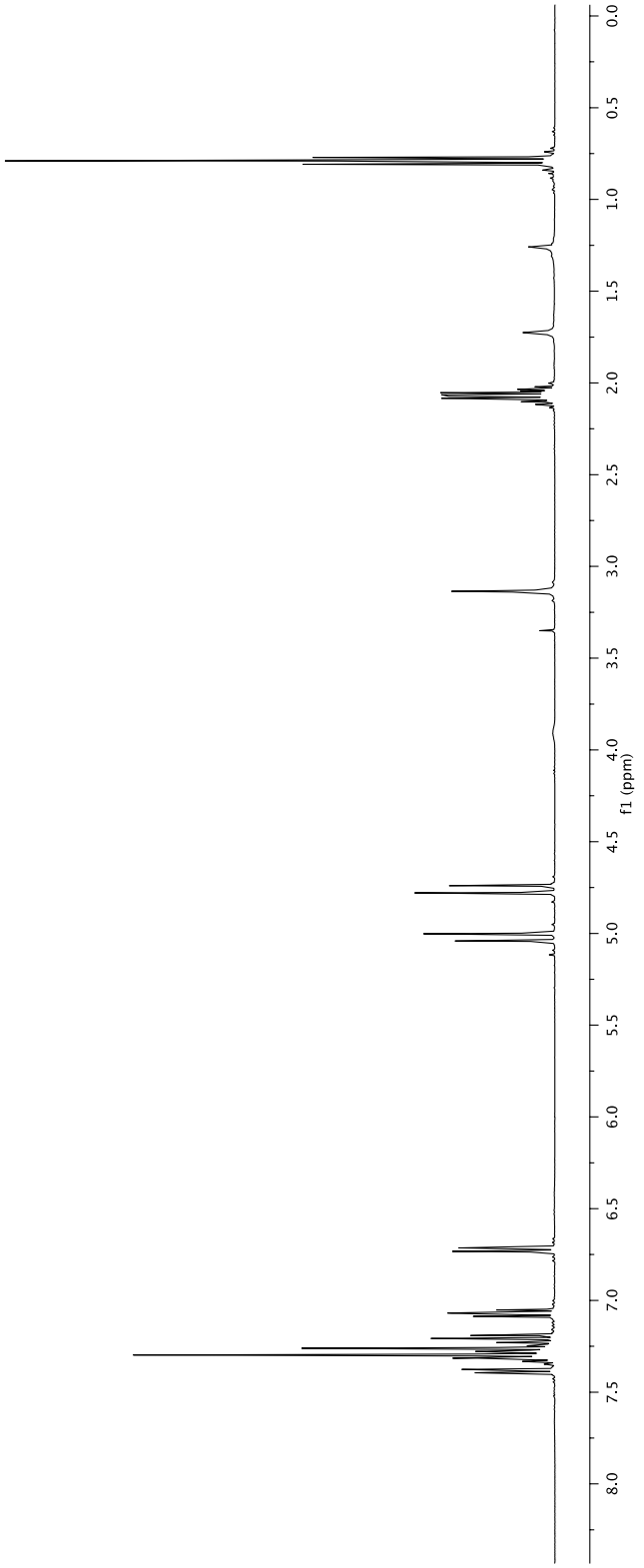
^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.38 (ddd, *J* = 7.3, 1.3, 0.5 Hz, 1H), 7.33 - 7.27 (m, 5H), 7.21 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.07 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.02 (d,

J = 15.7 Hz, 1H), 4.76 (d, *J* = 15.7 Hz, 1H), 2.88 (s, 1H), 2.06 (m, 2H), 0.79 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 178.3, 142.7, 135.5, 129.6, 129.5, 128.8, 127.7, 127.2, 123.9, 123.1, 109.4, 77.2, 43.8, 31.7, 7.7.

LRMS: (ESI) *m/z* 290.1 $[M+Na]^+$.

FTIR: (neat): 3312, 2962, 1692, 1616, 1492, 1355, 994, 755, 697 cm^{-1}.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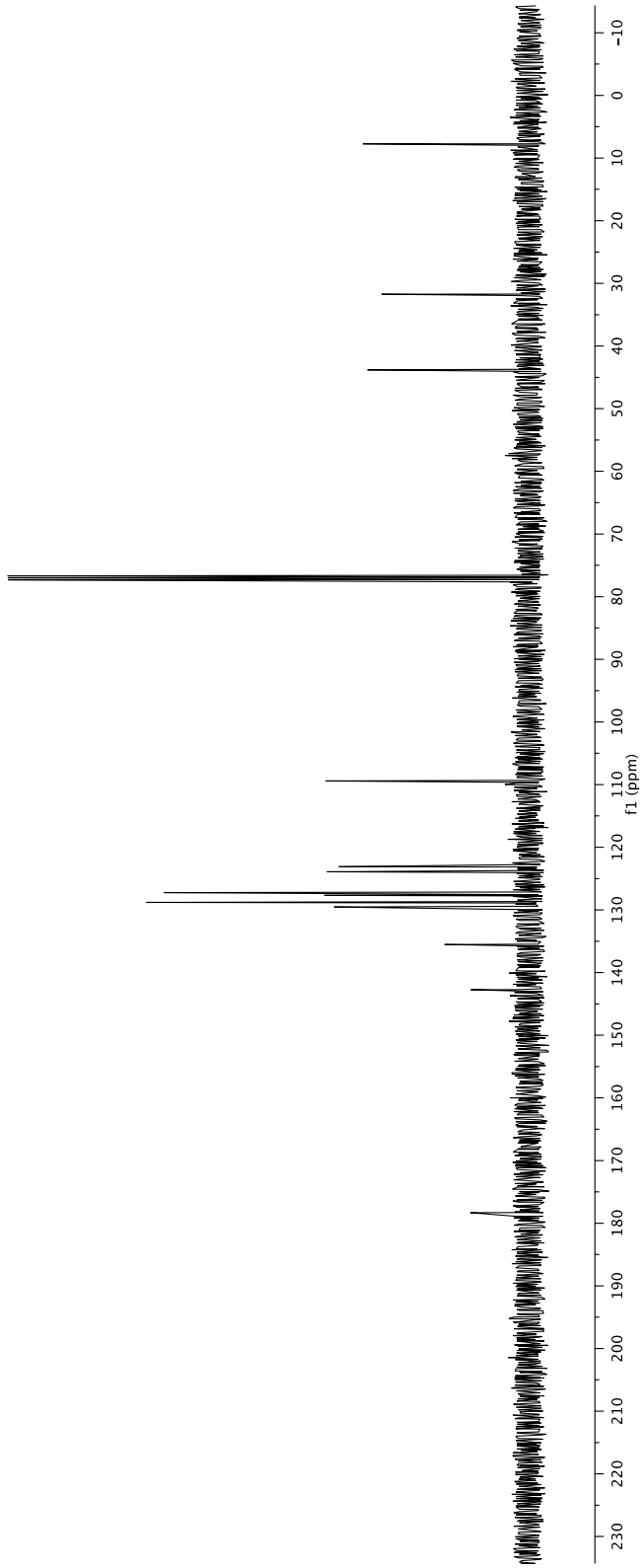
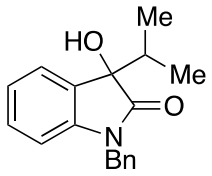
8.0
f1 (ppm)



1-

Benzyl-3-hydroxy-3-isopropylindolin-2-one (**2.3b**)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with propylene. *m*-Xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) was added and the reaction was purged again with propylene. The mixture was heated to 120 °C (oil bath temperature) for 24 h under an atmosphere of propylene, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole. The reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (SiO_2; dichloromethane:ethyl acetate = 97.5: 2.5 to 95:5) afforded the title compound (**2.3b**) (76mg, 0.27mmol, 90%) as a pale brown solid.

TLC (SiO_2): R_f = 0.14 (hexanes: ethyl acetate = 4:1).

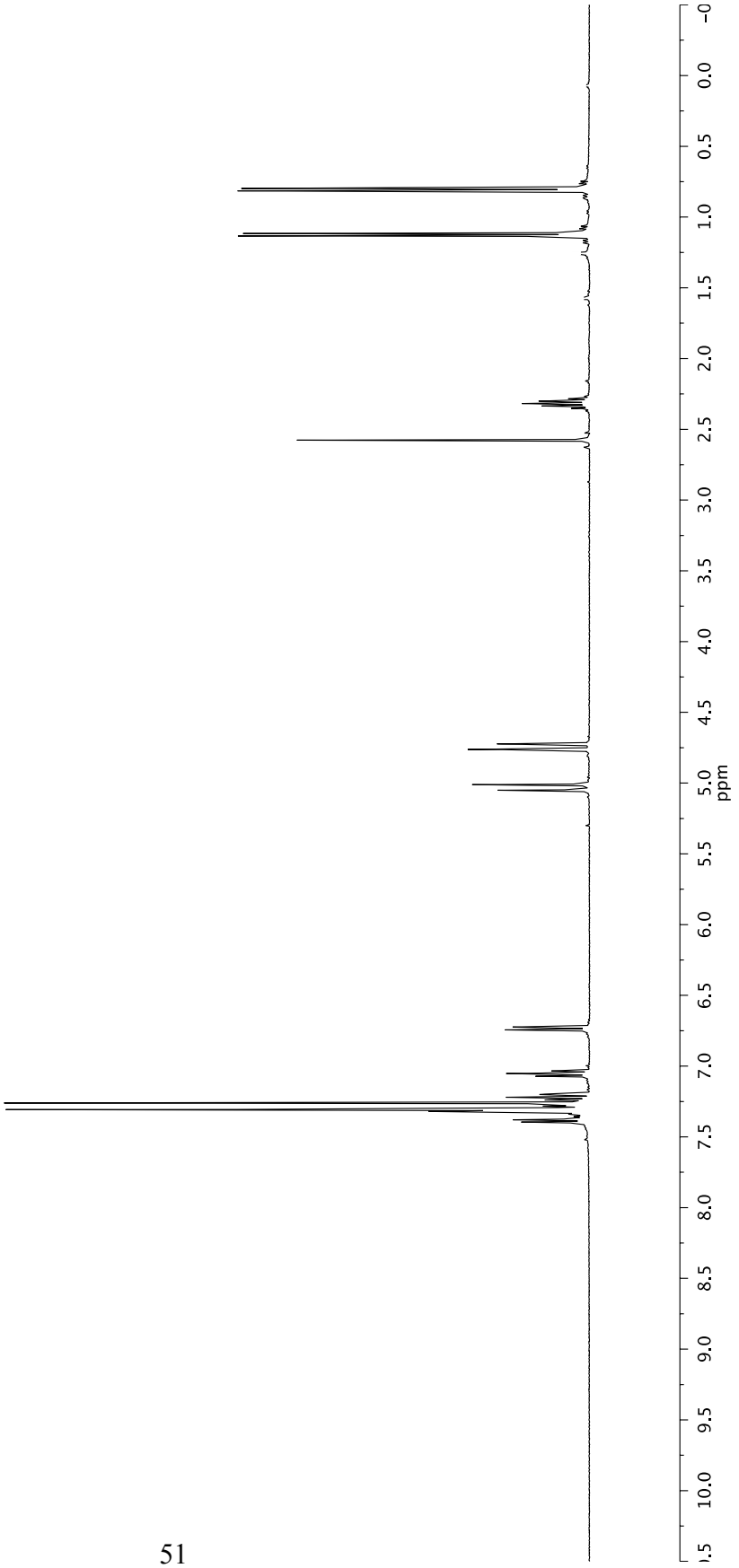
m.p.: 142-143 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.27 (m, 6H), 7.22 (td, *J* = 7.8, 1.3 Hz, 1H), 7.05 (td, *J* = 7.6, 1.0 Hz, 1H), 6.75 – 6.72 (m, 1H), 5.03 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 15.7 Hz, 1H), 2.58 (s, 1H), 2.32 (sept, *J* = 6.8 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5, 143.2, 135.6, 129.5, 128.8, 128.5, 127.7, 127.4, 124.7, 122.8, 109.3, 79.2, 43.9, 36.3, 16.5, 16.0.

LRMS (CI+) *m/z* 282 $[M+H]^+$.

FTIR (neat): 3359, 2966, 2929, 1695, 1614 1454, 1304, 1217, 1077, 752, 696 cm^{-1}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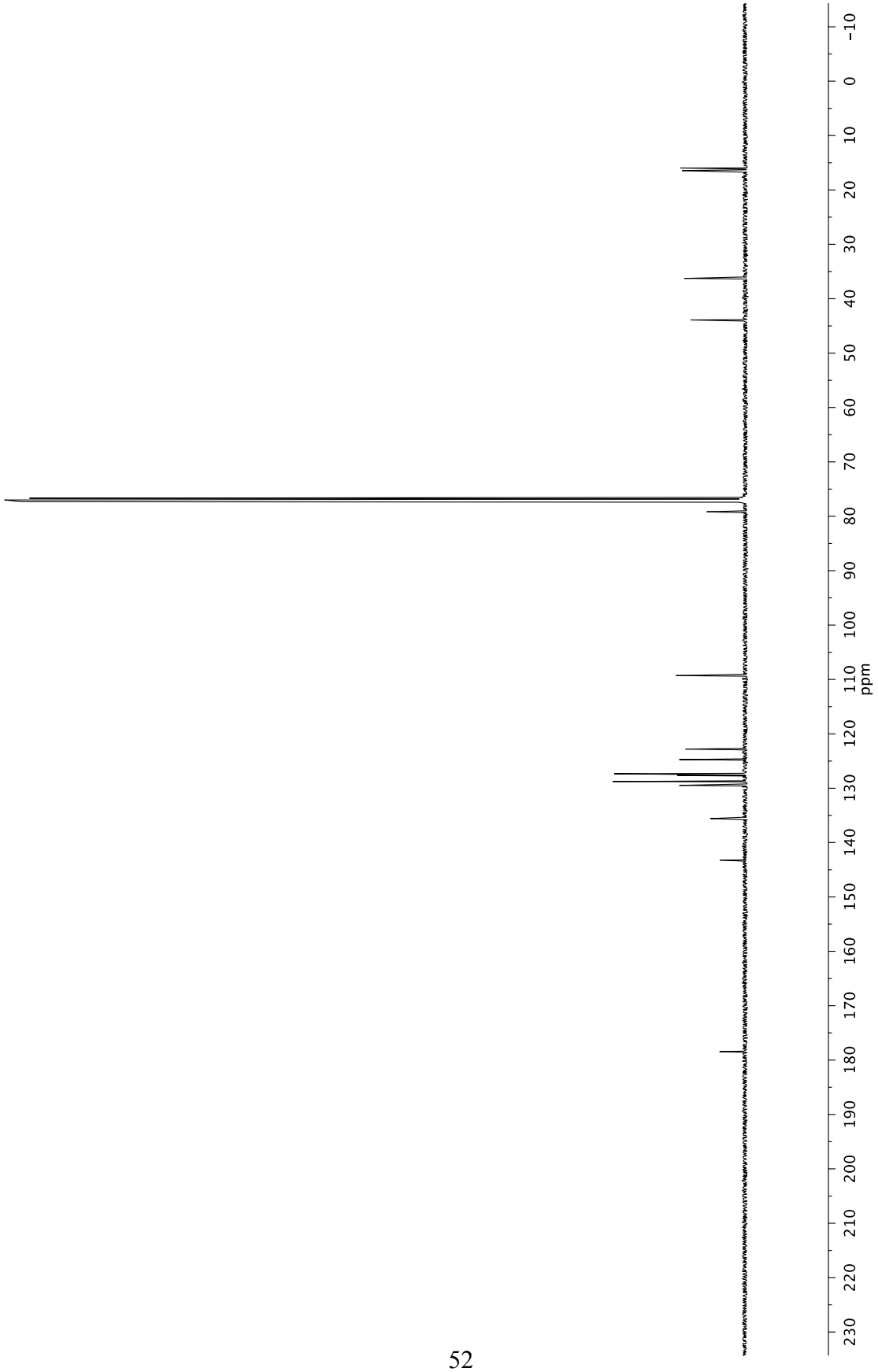
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30
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10
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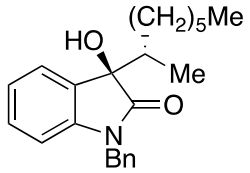
-10
ppm

(3*R)-1-Benzyl-3-hydroxy-3-((2*S**)-octan-2-yl)-indolin-2-one** (**2.3c**)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 1-Octene (**2.2c**) (141 μL, 0.9 mmol, 300 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated to 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 4:1) afforded the title compound (**2.3c**) (87 mg, 0.25 mmol, 83%) as a colorless solid.

TLC (SiO_2): R_f = 0.64 (hexanes:ethyl acetate = 1:1).

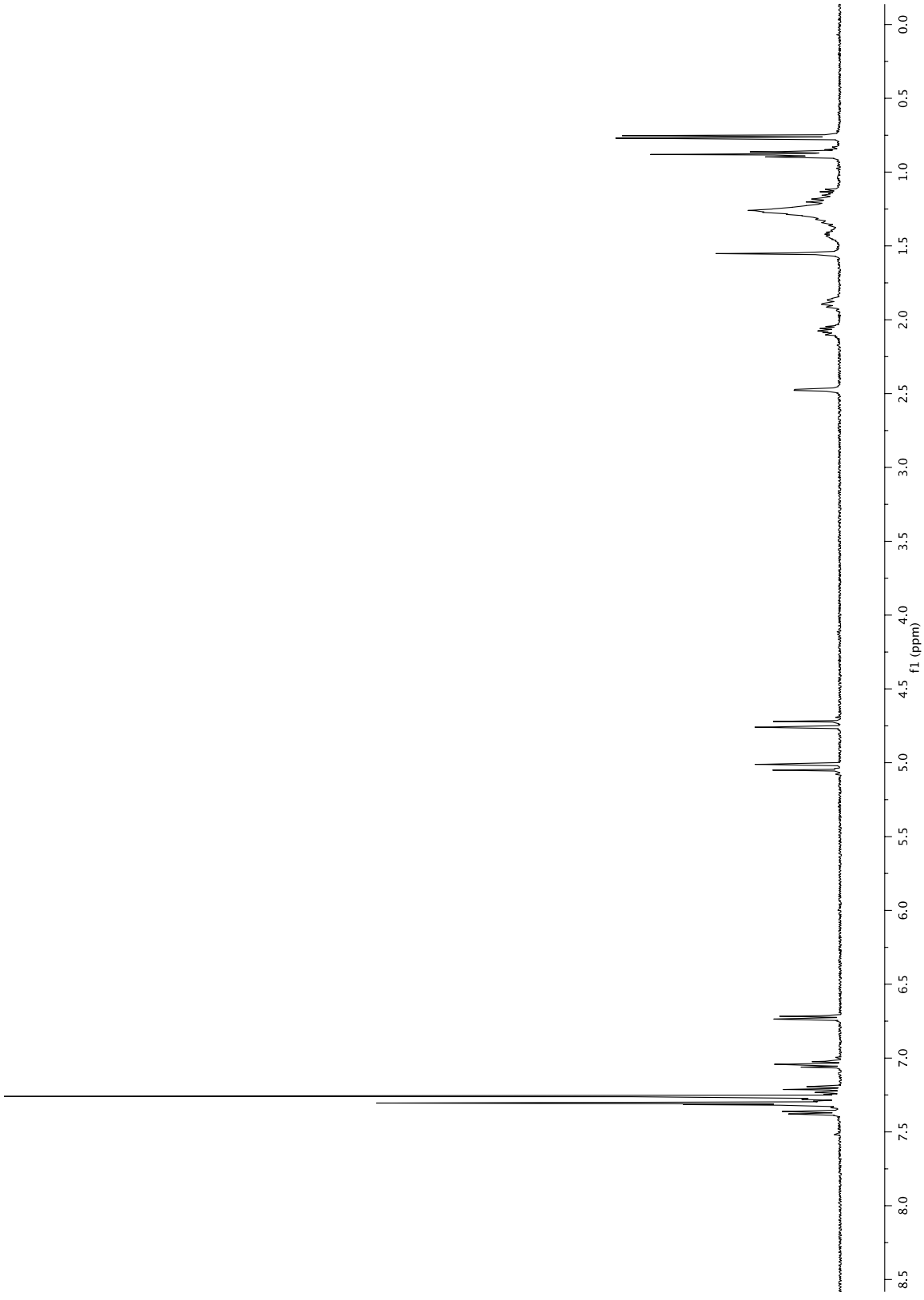
m.p.: 110-112ºC

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 6.5 Hz, 1H), 7.33 - 7.27 (m, 5H), 7.21 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H), 4.74 (d, *J* = 15.6 Hz, 1H), 2.48 (s, 1H), 2.07 (m, 1H), 1.89 (m, 1H), 1.42 (m, 1H), 1.38 - 1.11 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.76 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 178.7, 143.3, 135.6, 129.4, 128.8, 128.7, 127.6, 127.3, 124.9, 122.8, 109.3, 79.2, 43.9, 41.4, 31.8, 29.6, 29.4, 27.7, 22.6, 14.1, 13.5.

LRMS: (ESI) *m/z* 374.2 $[M+Na]^+$.

FTIR: (neat): 3346, 2958, 2853, 1700, 1616, 1491, 1371, 1102, 732, 697cm^{-1}.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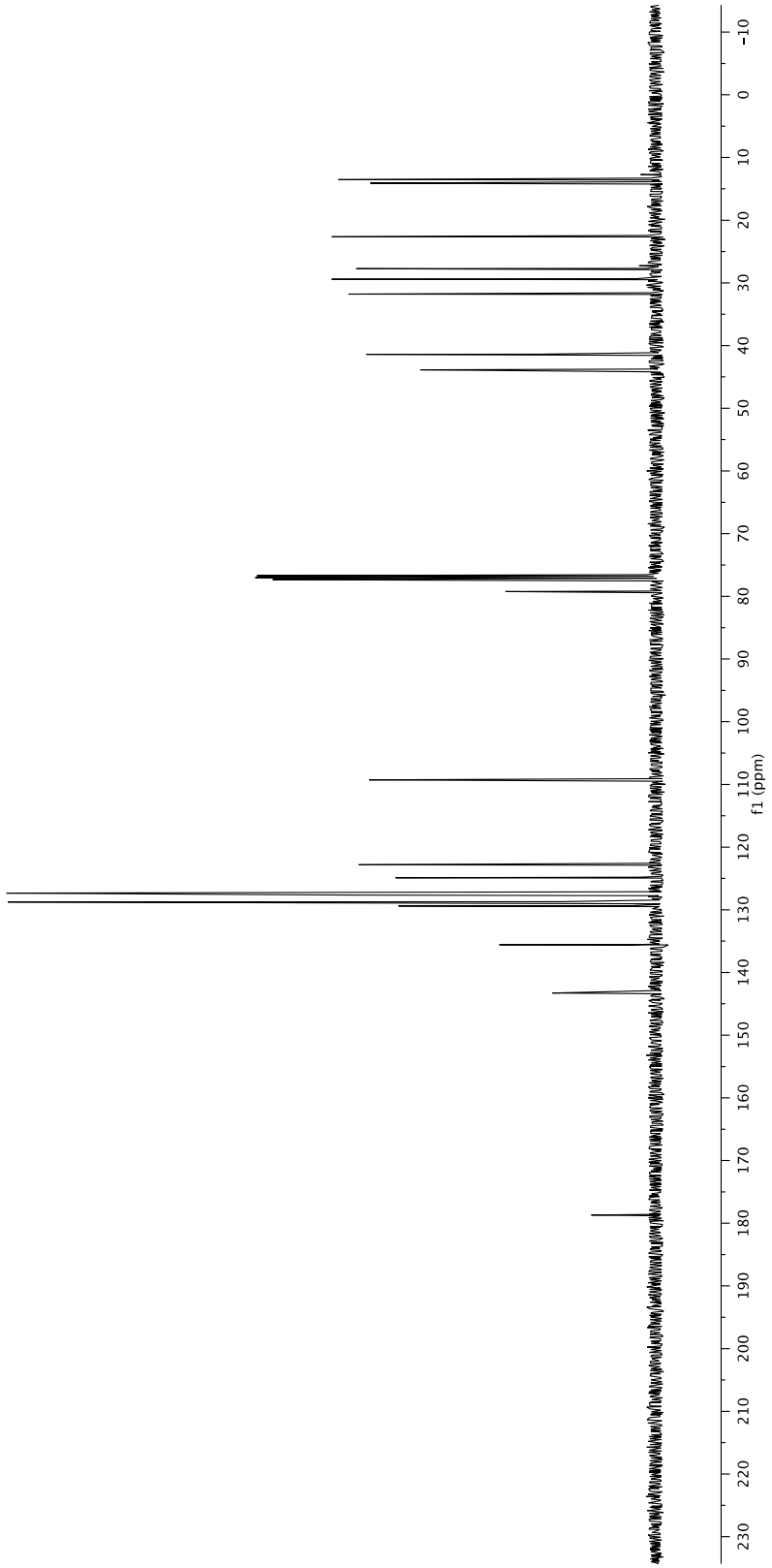
f1 (ppm)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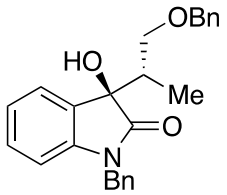
0
-10
f1 (ppm)

(3*R)-1-Benzyl-3-[(2*S**)-1-(benzyloxy)propan-2-yl]-3-hydroxyindolin-2-one** (**2.3d**)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. Allyl benzyl ether (**2.2d**) (133 mg, 0.9 mmol, 300 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3d**) (93 mg, 0.24 mmol, 80%) as a colorless solid.

TLC (SiO_2): R_f = 0.35 (hexanes:ethyl acetate = 2:1).

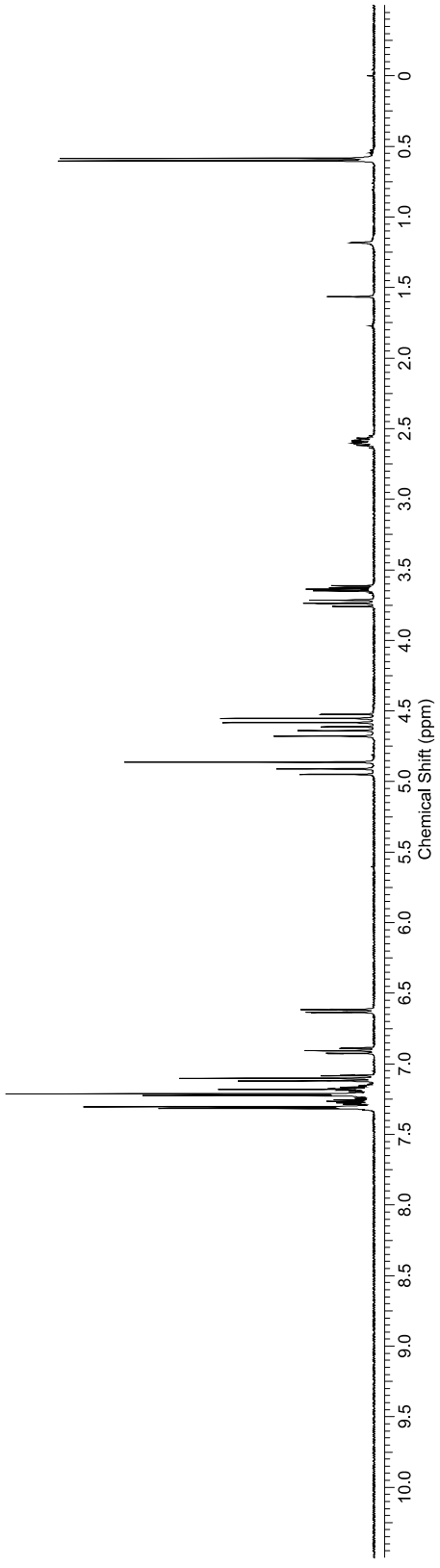
m.p.: 118-120 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 - 7.17 (m, 10H), 7.10 (t, *J* = 7.4 Hz, 2H), 6.91 (dd, *J* = 7.6, 7.4 Hz, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 4.93 (d, *J* = 15.7 Hz, 1H), 4.86 (s, 1H), 4.66 (d, *J* = 15.7 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 3.74 (d, *J* = 9.5, 8.6 Hz, 1H), 3.63 (dd, *J* = 9.5, 5.9 Hz, 1H), 2.59 (ddq, *J* = 8.6, 6.9, 5.9 Hz, 1H), 0.63 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 143.1, 137.2, 135.7, 129.3, 128.9, 128.8, 128.6, 128.1, 128.0, 127.6, 127.4, 124.9, 122.7, 109.3, 79.6, 73.7, 72.4, 43.9, 39.3, 11.9.

LRMS (ESI) *m/z* 410.2 $[M+Na]^+$.

FTIR (neat): 3423, 1715, 1612, 1488, 1466, 1361, 1178, 1074, 908, 733 cm^{-1}.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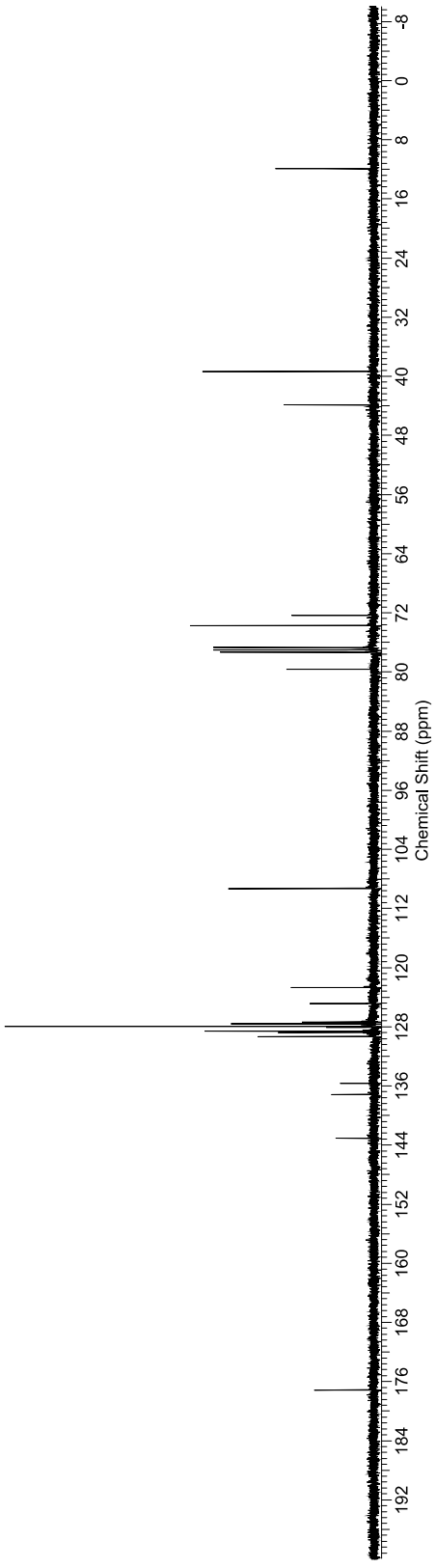
Chemical Shift (ppm)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120
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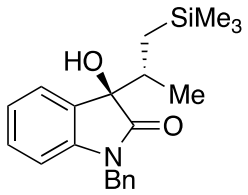
144
152
160
168
176
184
192
Chemical Shift (ppm)

(3*R)-1-Benzyl-3-hydroxy-3-((2*R**)-1-(trimethylsilyl)propan-2-yl)indolin-2-one** (**2.3e**)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. Allyltrimethylsilane (**2.2e**) (143 μL, 0.9 mmol, 300 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; dichloromethane:ethyl acetate = 97.5: 2.5) afforded the title compound (**2.3e**) (101 mg, 0.29 mmol, 95%) as a colorless solid.

TLC (SiO_2): R_f = 0.29 (hexanes: ethyl acetate = 4:1).

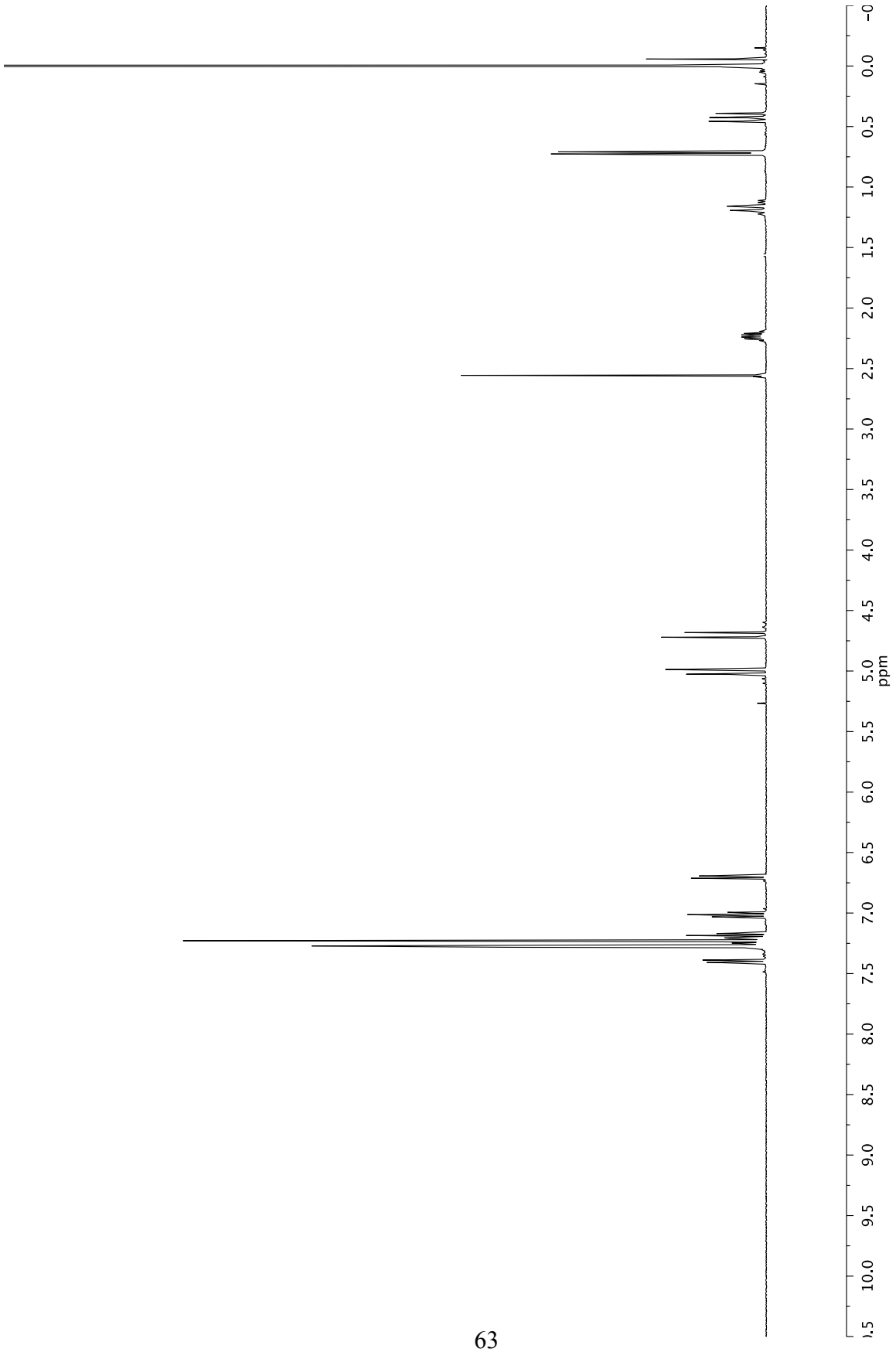
m.p.: 162-163 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 7.4, 1.3 Hz, 2H), 7.28 - 7.24 (m, 4H), 7.19 (ddd, *J* = 7.8, 7.6, 1.3 Hz, 1H), 7.01 (td, *J* = 7.6, 1.0 Hz, 1H), 6.70 (dd, *J* = 7.8, 0.9 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 4.70 (d, *J* = 15.6 Hz, 1H), 2.56 (s, 1H), 2.31 – 2.09 (m, 1H), 1.26 – 1.03 (m, 1H), 0.72 (d, 3H), 0.52 – 0.32 (m, 1H), 0.00 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6, 144.1, 136.4, 130.2, 129.5, 129.3, 128.4, 128.2, 125.7, 123.5, 110.0, 80.4, 44.7, 38.8, 17.7, 17.1, 0.0.

LRMS (CI+) *m/z* 354 $[M+H]^+$.

FTIR (neat): 3352, 2952,1697, 1617 1416, 1214, 1134, 1101, 858, 798 cm^{-1}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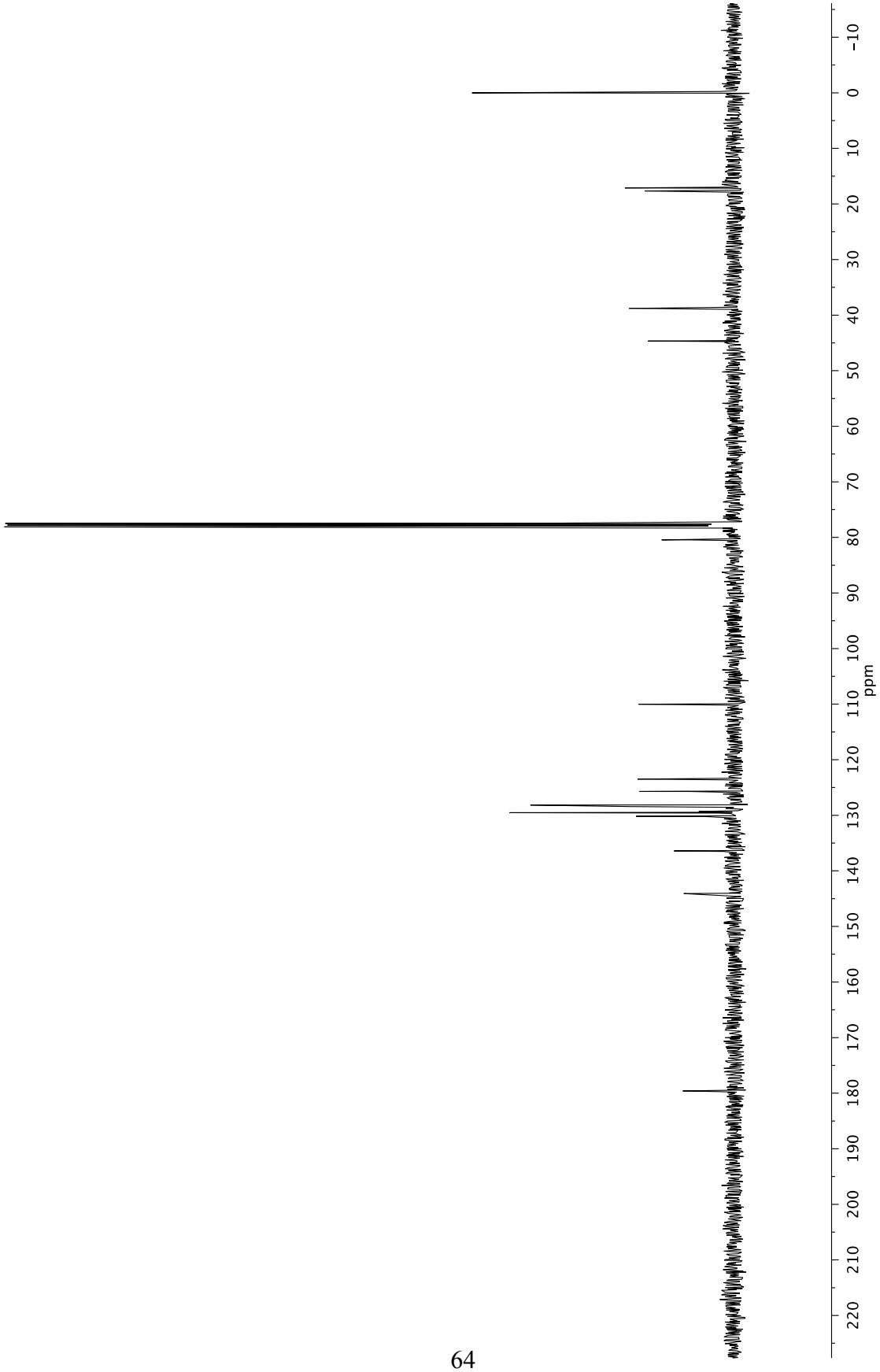
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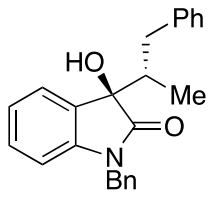
140
150
160
170
180
190
200
210
220
ppm

(3*R)-1-Benzyl-3-hydroxy-3-((2*S**)-1-phenylpropan-2-yl)indolin-2-one (2.3f)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. Allylbenzene (**2.3f**) (119 μL, 0.9 mmol, 300 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = 14:1 as determined by ^{1}H NMR spectroscopy). Purification of crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3f**) (101 mg, 0.28 mmol, 94%) as a colorless solid.

TLC (SiO_2): R_f = 0.45 (hexanes:ethyl acetate = 2:1).

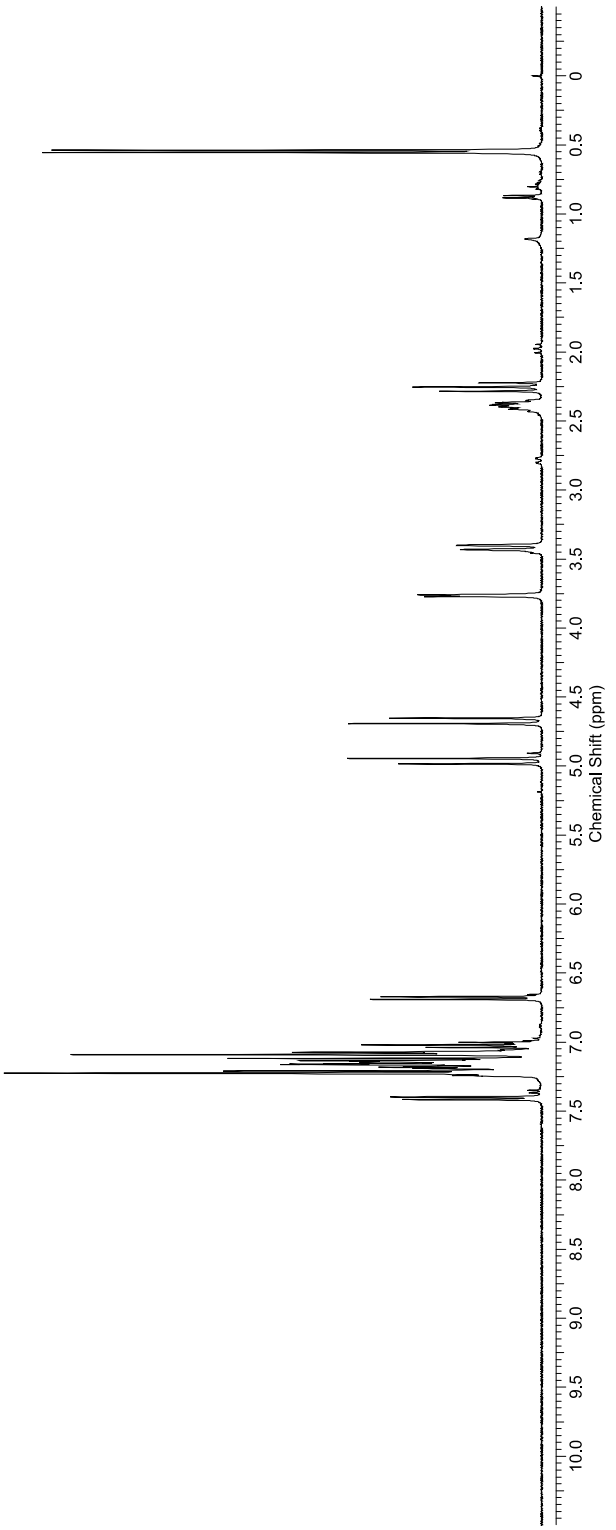
m.p.: 139-141 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.37 - 7.23 (m, 8H), 7.20 - 7.16 (m, 3H), 7.12 (dt, *J* = 7.6, 1.0 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 5.06 (d, *J* = 15.7 Hz, 1H), 4.78 (d, *J* = 15.7 Hz, 1H), 3.76 (br. s, 1H), 3.43 - 3.40 (m, 1H), 2.43 - 2.22 (m, 2H), 0.65 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 143.3, 140.4, 135.5, 129.6, 129.3, 128.8, 128.5, 128.3, 127.7, 127.4, 126.0, 125.0, 123.1, 109.5, 79.3, 43.9, 43.8, 36.1, 13.0.

LRMS (ESI) *m/z* 380.2 $[M+Na]^+$.

FTIR (neat): 3405, 1699, 1613, 1488, 1368, 1176, 730, 689 cm^{-1}.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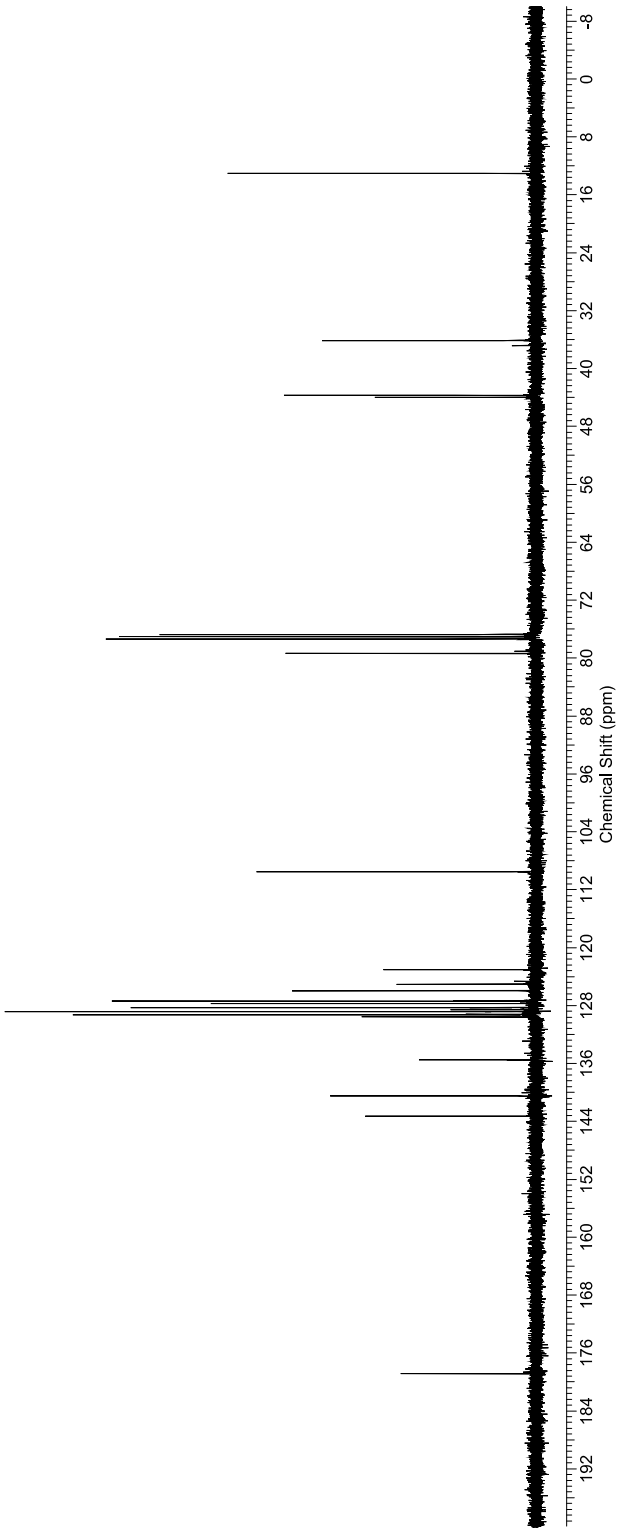
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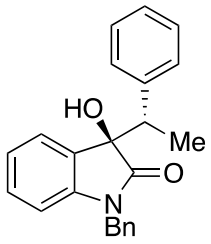
Chemical Shift (ppm)

(3*R)-1-Benzyl-3-hydroxy-3-((1*S**)-1-phenylethyl)indolin-2-one (2.3g)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. Styrene (**2.2g**) (160 µL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3g**) (98 mg, 0.28 mmol, 94%) as a colorless solid.

TLC (SiO_2): R_f = 0.30 (hexanes:ethyl acetate = 2:1).

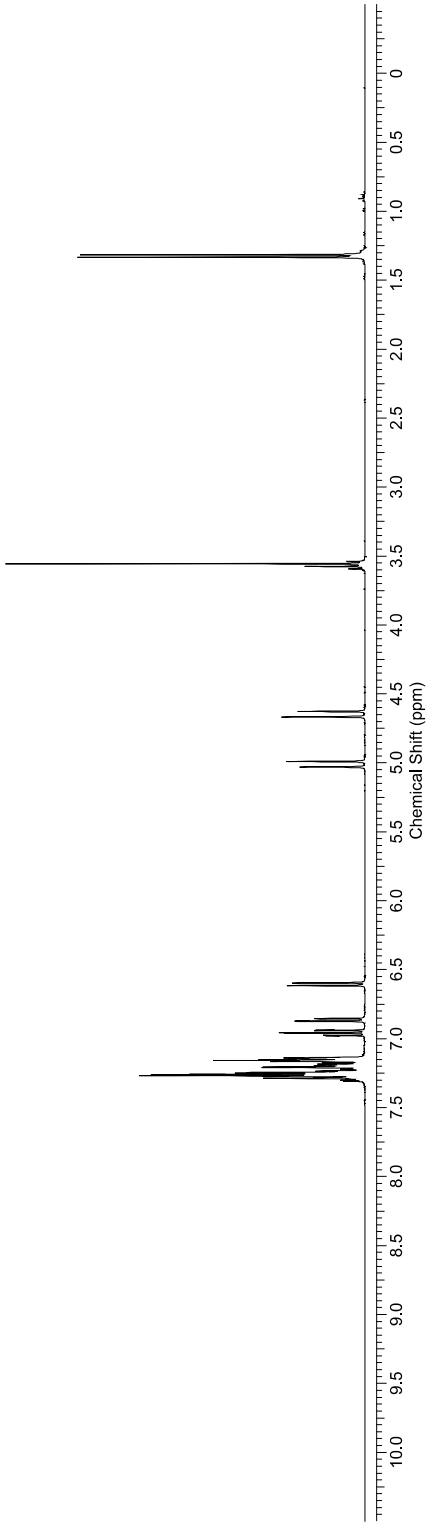
m.p.: 118-120 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 - 7.14 (m, 11H), 6.96 (ddd, *J* = 7.6, 7.4, 1.0 Hz, 1H), 6.86 (dd, *J* = 7.2, 1.1 Hz, 1H), 6.61 (d, *J* = 7.4 Hz, 1H), 5.02 (d, *J* = 15.7 Hz, 1H), 4.64 (d, *J* = 15.7 Hz, 1H), 3.58 (q, *J* = 7.2 Hz, 1H), 3.56 (s, 1H), 1.33 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 143.1, 139.4, 135.4, 129.5, 129.5, 128.8, 128.6, 127.7, 127.6, 127.3, 127.1, 125.2, 122.6, 109.2. 78.8, 46.3, 44.0, 14.0.

LRMS (ESI) *m/z* 366.1 $[M+Na]^+$.

FTIR (neat): 3386, 2929, 1697, 1613, 1489, 1466, 1368, 1174, 700 cm^{-1}.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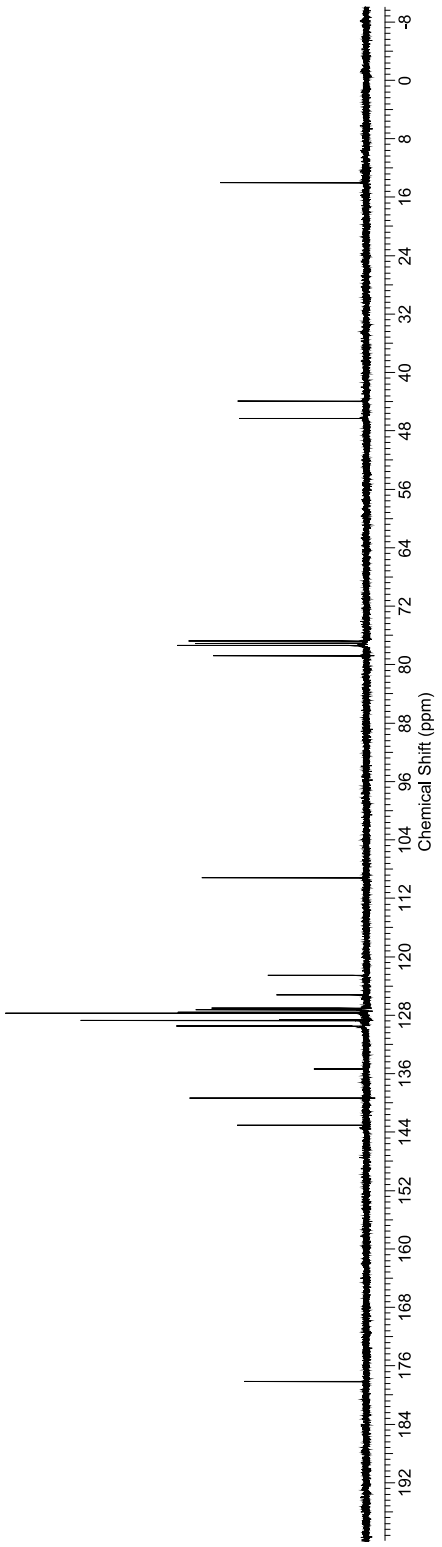
Chemical Shift (ppm)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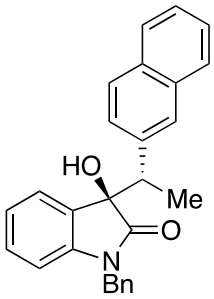
Chemical Shift (ppm)

(3*R)-1-Benzyl-3-hydroxy-3-[(1*S**)-1-(naphthalen-2-yl)ethyl]indolin-2-one (2.3h)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 2-Vinylnaphthalene (**2.2h**) (185 mg, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24 hrs, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = 12:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3h**) (96 mg, 0.24 mmol, 81%) as a colorless solid.

TLC (SiO_2): R_f = 0.30 (hexanes:ethyl acetate = 2:1).

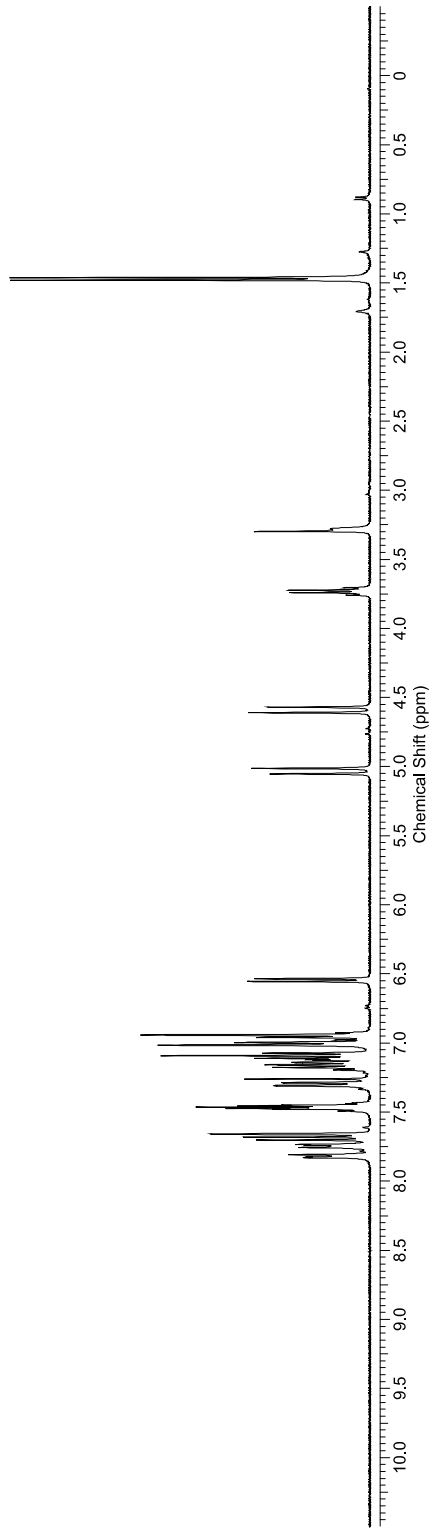
m.p.; 148-150 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 - 7.75 (m, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.50 - 7.44 (m, 2H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.20-7.08 (m, 4H), 7.01 (d, *J* = 7.6 Hz, 2H), 6.98 - 6.93 (m, 2H), 6.55 (d, *J* = 7.8 Hz, 1H), 5.04 (d, *J* = 15.7 Hz, 1H), 4.59 (d, *J*= 15.7 Hz, 1H), 3.75 (q, *J* = 7.2 Hz, 1H), 3.47 (br. s, 1H), 1.47 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 143.1, 137.0, 135.2, 133.0, 132.6, 129.6, 128.8, 128.6, 128.2, 128.0, 127.9, 127.5, 127.5, 127.1, 127.0, 125.9, 125.8, 125.1, 122.6, 109.3, 78.9, 46.5, 44.0, 14.2.

LRMS (CI+) *m/z* 394 $[M+H]^+$.

FTIR (neat): 3056, 1679, 1613, 1488, 1366, 1172, 1029, 734 cm^{-1}.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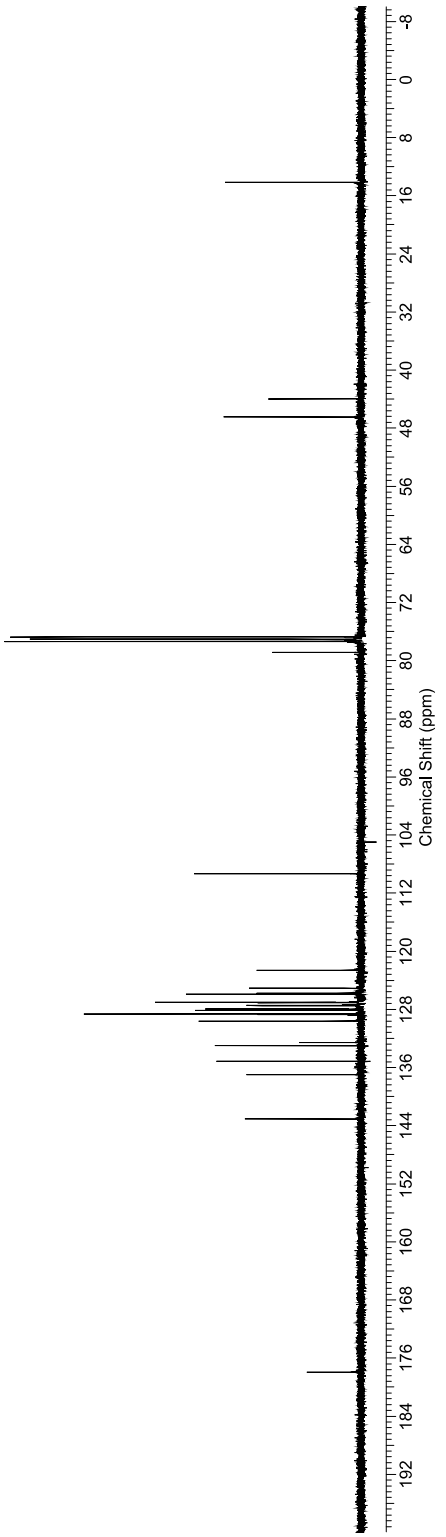
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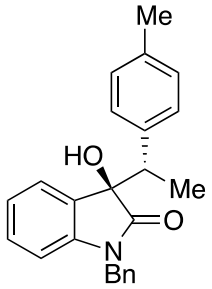
Chemical Shift (ppm)

(3*R)-1-Benzyl-3-hydroxy-3-((1*S**)-1-(*p*-tolyl)ethyl)indolin-2-one (2.3i)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 4-Methylstyrene (**2.2i**) (158 μL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3i**) (89 mg, 0.25 mmol, 83%) as a colorless solid.

TLC (SiO_2): R_f = 0.30 (hexanes:ethyl acetate = 2:1).

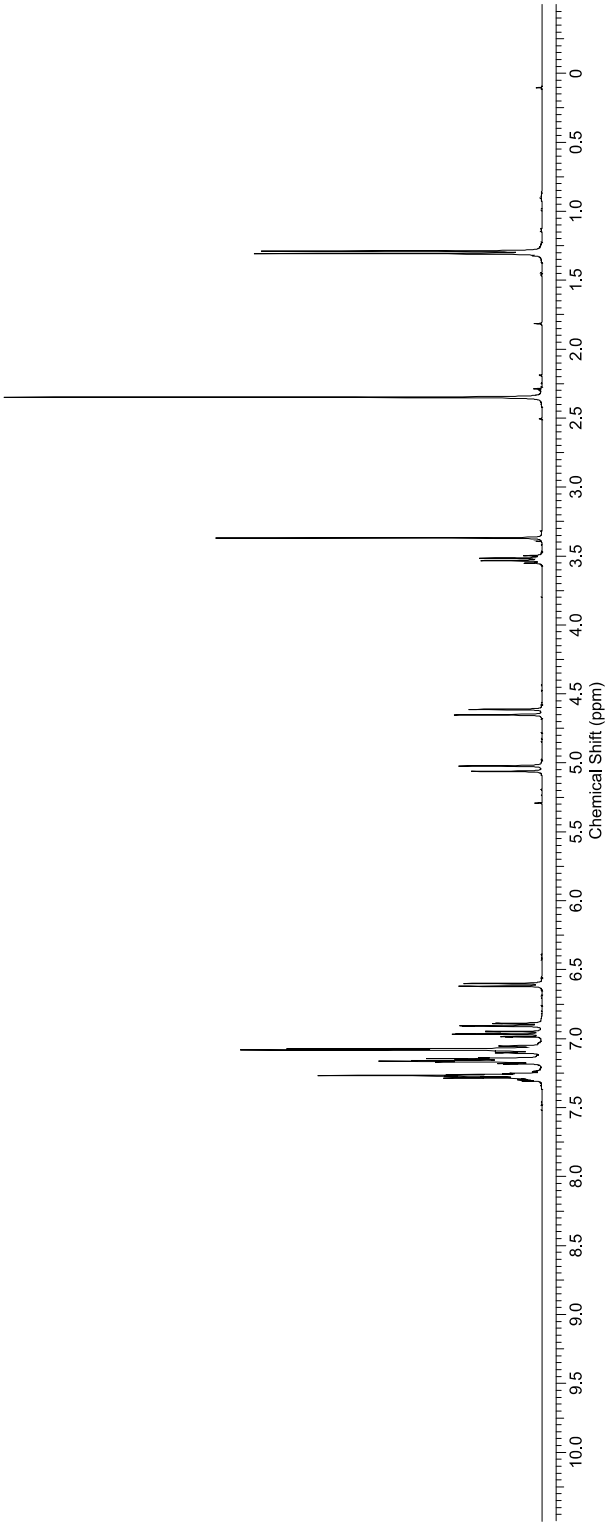
m.p.; 151-152 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 - 7.25 (m, 3H), 7.19 - 7.14 (m, 3H), 7.09 - 7.07 (m, 4H), 6.97 (ddd, *J* = 8.4, 7.4, 0.9 Hz, 1H), 6.90 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.61 (dd, *J* = 7.8, 0.9 Hz, 1H), 5.03 (d, *J* = 15.9 Hz, 1H), 4.63 (d, *J* = 15.9 Hz, 1H), 3.49 (q, *J* = 7.2 Hz, 1H), 2.78 (s. 1H), 2.35 (s, 3H), 1.30 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 143.1, 136.7, 136.2, 135.4, 129.5, 129.3, 128.7, 128.6, 128.5, 127.6, 127.3, 125.1, 122.5, 109.2, 78.6, 45.9, 43.9, 21.1, 14.1.

LRMS (CI+) *m/z* 358.2 $[M+H]^+$.

FTIR (neat): 3393, 3024, 1699, 1614, 1488, 1467, 1369, 1173, 819, 750 cm^{-1}.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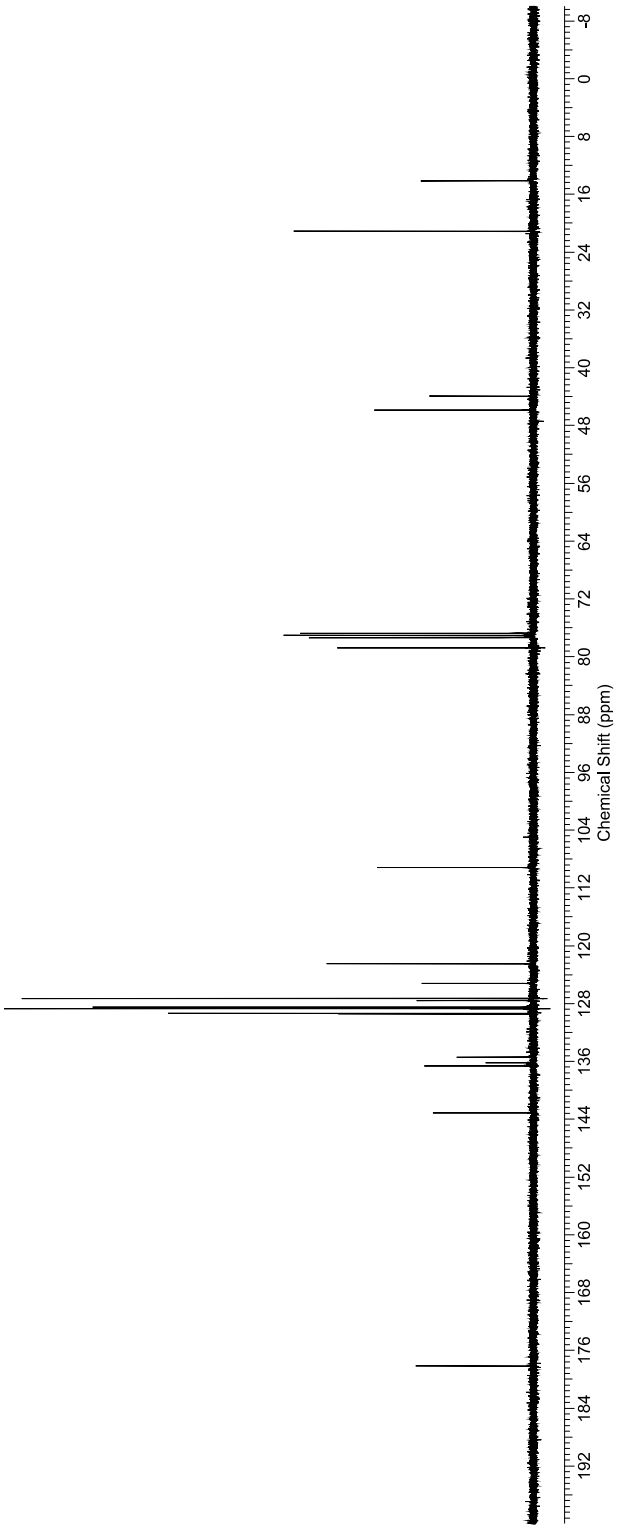
Chemical Shift (ppm)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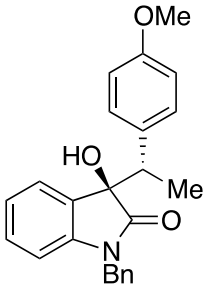
Chemical Shift (ppm)

(3*R)-1-benzyl-3-hydroxy-3-[(1*S**)-1-(4-methoxyphenyl)ethyl]-indolin-2-one (2.3j)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 4-vinylanisole (**2.2j**) (160 µL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated to 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2.5:1) afforded the title compound (**2.3j**) (86 mg, 0.23 mmol, 77%) as a colorless solid.

TLC (SiO_2): R_f = 0.24 (hexanes:ethyl acetate = 2:1).

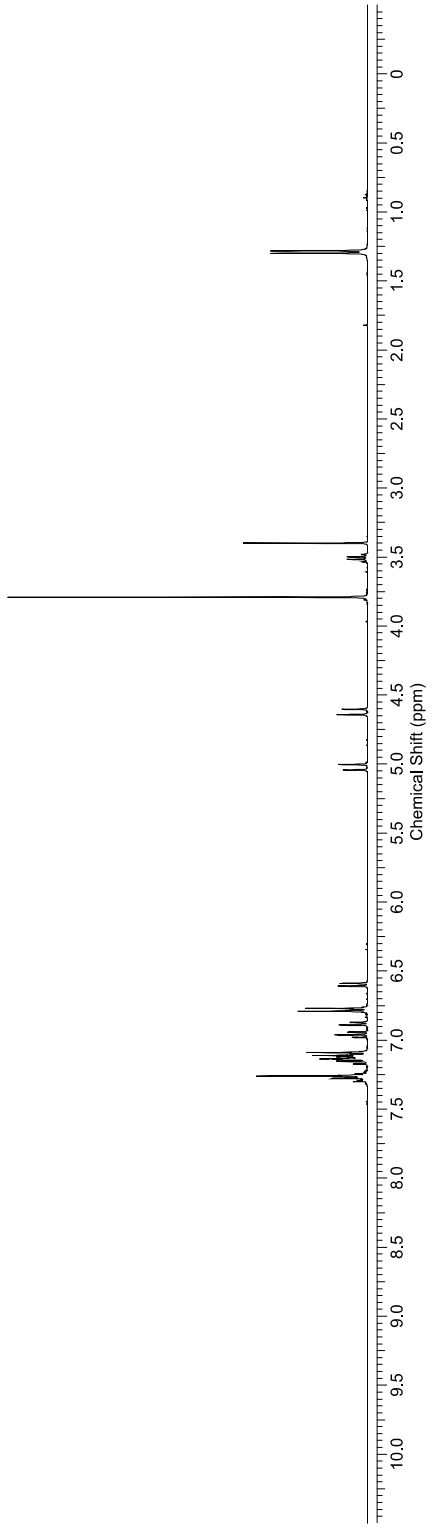
m.p.: 141-143ºC

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, 2H), 7.19 - 7.05 (m, 6H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.02 (d, *J* = 15.8 Hz, 1H), 4.63 (d, *J* = 15.8 Hz, 1H), 3.79 (s, 3H), 3.49 (q, *J* = 7.0 Hz, 1H), 3.18 (s, 1H), 1.29 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 178.1, 158.6, 143.0, 135.3, 131.2, 130.4, 129.4, 128.8, 128.6, 127.5, 127.2, 125.1, 122.5, 113.1, 109.2, 78.8, 55.1, 45.4, 43.9, 14.1.

LRMS: (ESI) *m/z* 396.2 $[M+Na]^+$.

FTIR: (neat): 3412, 2984, 1698, 1616, 1454, 1372, 1248, 1173, 1023, 832, 705 cm^{-1}.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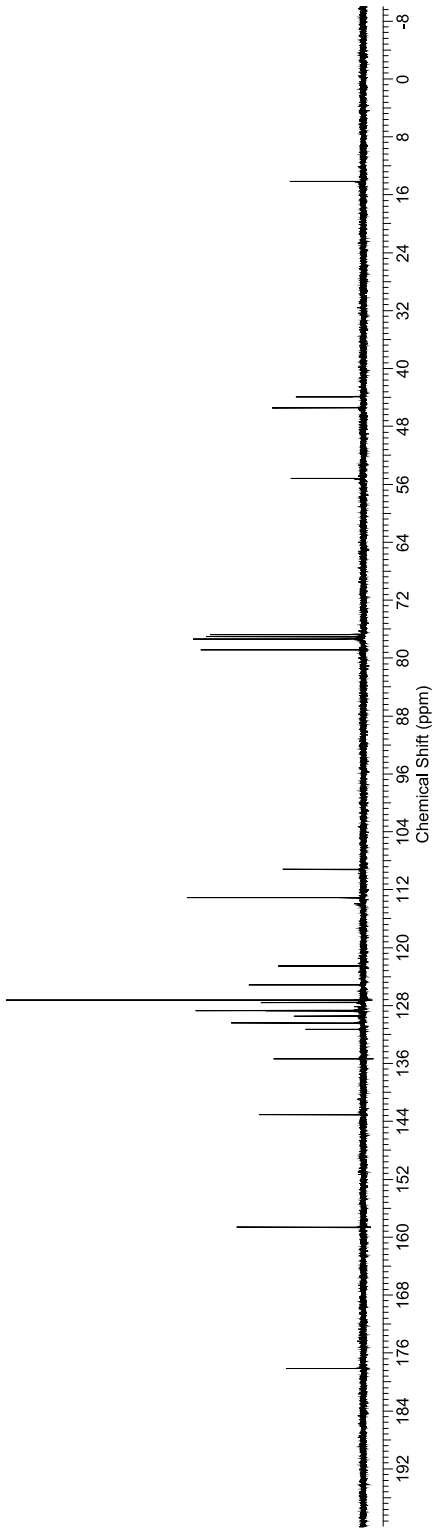
Chemical Shift (ppm)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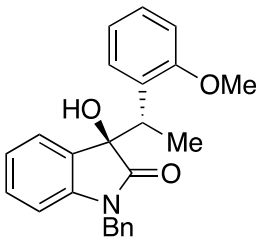
Chemical Shift (ppm)

(3*R)-1-benzyl-3-hydroxy-3-[(1*S**)-1-(2-methoxyphenyl)ethyl]-indolin-2-one (2.3k)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 2-Vinylanisole (**2.2k**) (161 μL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated to 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (r.r (branched:linear) = 1.3:1, d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2.5:1) afforded the title compound (**2.3k**) (58 mg, 0.16 mmol, 52%) and the linear isomer 1-benzyl-3-hydroxy-3-(2-methoxyphenethyl)indolin-2-one (44 mg, 0.12 mmol, 39%) as colorless solids in 91% overall yield.

TLC (SiO_2): R_f = 0.52 (hexanes:ethyl acetate = 1:1).

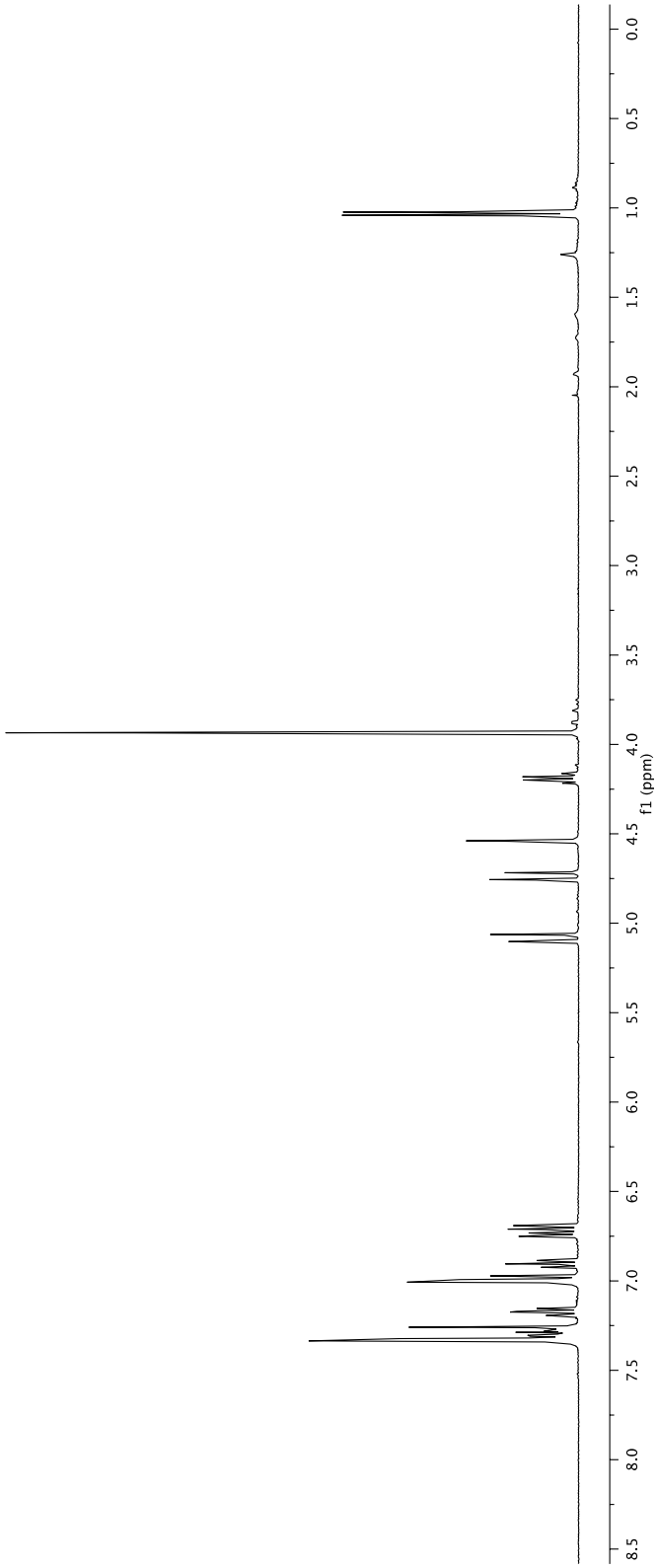
m.p.: 140-142ºC

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.36 - 7.26 (m, 6H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1H), 7.03 - 6.96 (m, 3H), 6.91 (td, *J* = 7.6, 0.9 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.08 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 15.7 Hz, 1H), 4.54 (s, 1H), 4.19 (q, *J* = 7.2 Hz, 1H), 3.94 (s, 3H), 1.03 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 178.8, 157.4, 143.4, 135.7, 129.3, 129.2, 128.7, 128.2, 128.2, 127.7, 127.6, 127.4, 125.8, 122.2, 120.7, 110.7, 108.9, 80.1, 55.7, 43.9, 37.3, 14.5.

LRMS: (ESI) *m/z* 396.2 $[M+Na]^+$.

FTIR: (neat): 3479, 2943, 1710, 1612, 1488, 1231, 1020, 719, 699 cm^{-1}.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7.0
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5.5
5.0
4.5
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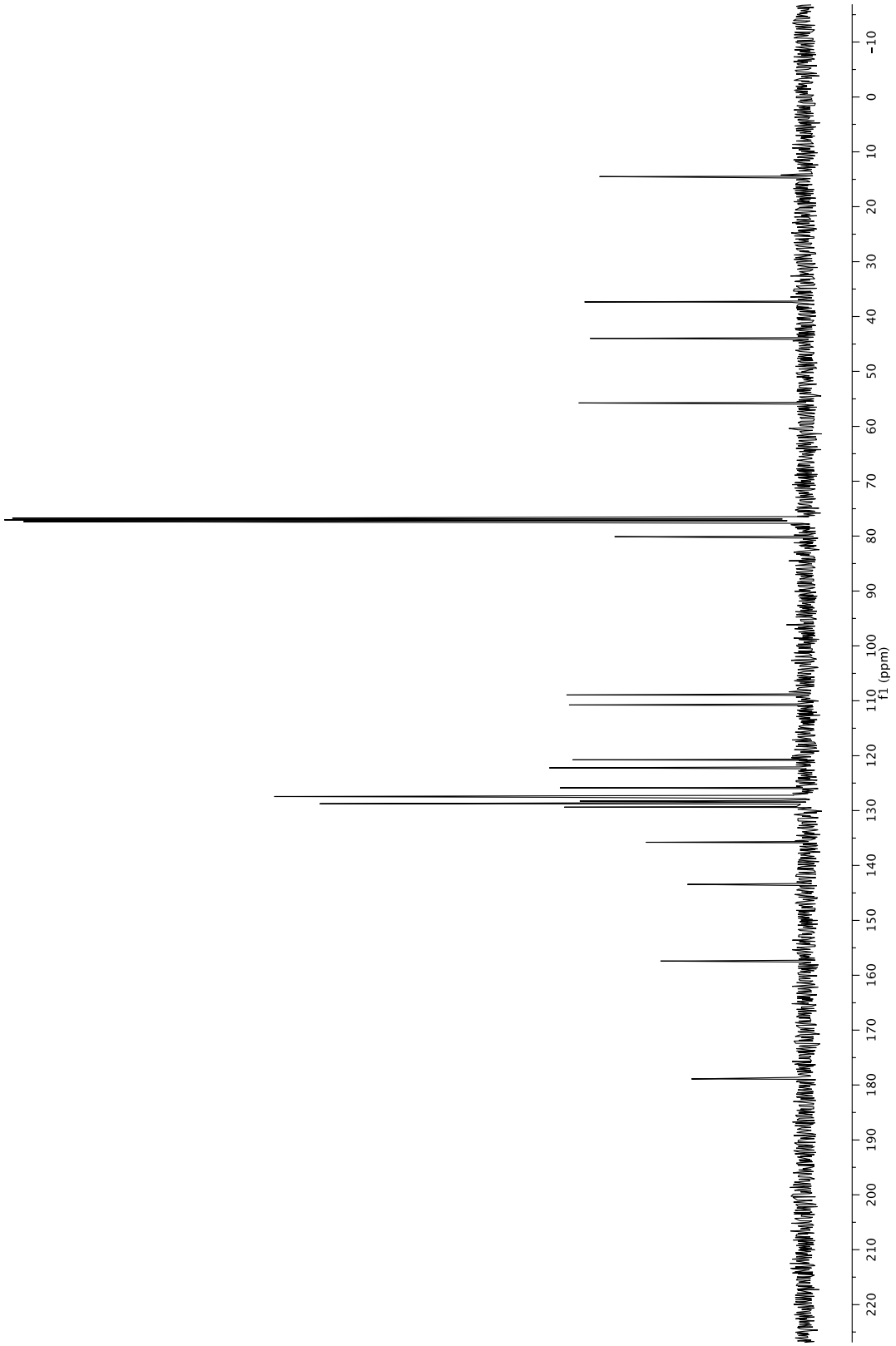
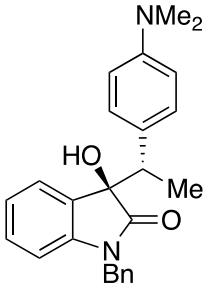
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


f1 (ppm)

(3*R)-1-benzyl-3-hydroxy-3-[(1*S**)-1-(4-(dimethylamino)phenyl)ethyl]-indolin-2-one (2.3l)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. *N*,*N*-dimethyl-4-vinylaniline (**2.2l**) (184 μL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated to 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2.5:1) afforded the title compound (**2.3l**) (75 mg, 0.20 mmol, 65%) as a colorless solid.

TLC (SiO_2): R_f = 0.31 (hexanes:ethyl acetate = 1:1).

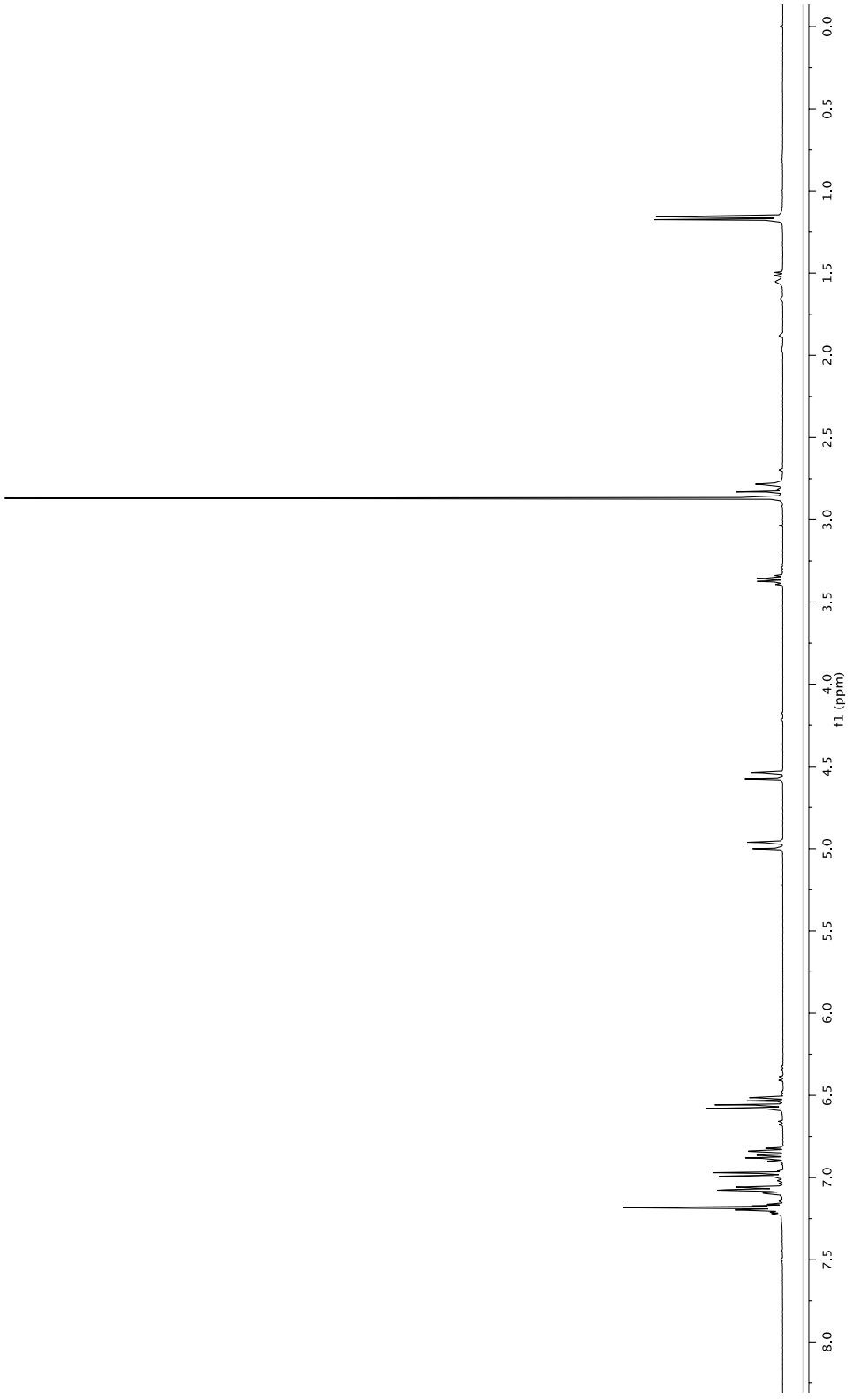
m.p.: 171-173ºC

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.30 - 7.23 (m, 3H), 7.15 (m, 3H), 7.05 (d, *J* = 8.7 Hz, 2H), 6.96 (dt, *J* = 7.4, 0.9 Hz, 1H), 6.92 (dt, *J* = 7.4, 1.4 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 15.8 Hz, 1H), 4.63 (d, *J* = 15.8 Hz, 1H), 3.43 (q, *J* = 7.2 Hz, 1H), 2.94 (s, 6H), 2.70 (s, 1H), 1.24 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 178.1, 149.7, 143.1, 135.4, 130.0, 129.3, 128.9, 128.6, 127.5, 127.2, 126.7, 125.2, 122.4, 112.0, 109.1, 78.9, 45.3, 43.9, 40.6, 14.1.

LRMS: (CI+) *m/z* 409.2 $[M+Na]^+$.

FTIR: (neat): 3397, 2967, 1697, 1613, 1525, 1466, 1374, 1170, 948, 725 cm^{-1}.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4.5
4.0
3.5
3.0
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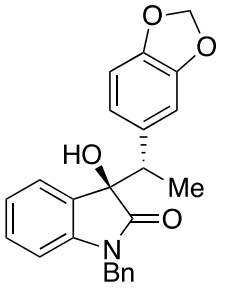
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

(3*R)-3-[(1*S**)-1-(2H-1,3-benzodioxol-5-yl)ethyl]-1-benzyl-3-hydroxy-indolin-2-one (2.3m)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 5-ethenyl-2H-1,3-benzodioxole (**2.2m**) (154 µL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated to 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2.5:1) afforded the title compound (**2.3m**) (94 mg, 0.24 mmol, 81%) as a colorless solid.

TLC (SiO_2): R_f = 0.25 (hexanes:ethyl acetate = 2:1).

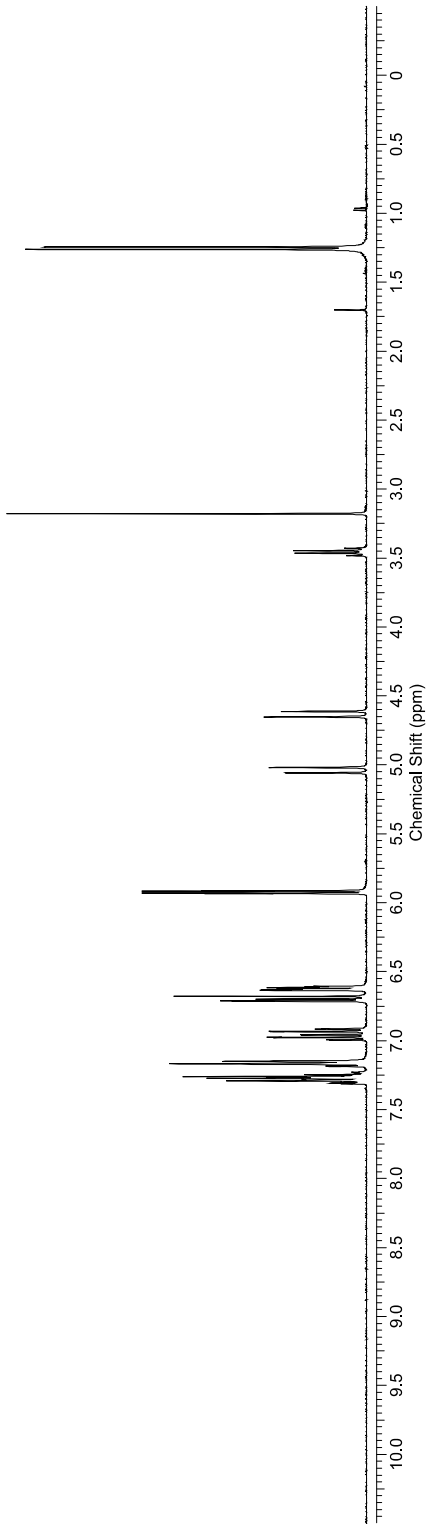
m.p.: 121-123 ºC

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.32 - 7.24 (m, 3H), 7.17 (m, 3H), 6.98 (t, *J* = 7.4 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.69 (m, 2H), 6.62 (m, 2H), 5.93 (dd, *J* = 6.6, 1.3 Hz, 2H), 5.03 (d, *J* = 15.8 Hz, 1H), 4.64 (d, *J* = 15.8 Hz, 1H), 3.44 (q, *J* = 7.1 Hz, 1H), 2.84 (br. s, 1H), 1.26 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 178.0, 147.1, 146.6, 143.1, 135.3, 133.1, 129.6, 128.7, 128.5, 127.6, 127.2, 125.1, 122.6, 122.6, 109.9, 109.3, 107.6, 100.9, 78.6, 46.0, 43.9, 14.3.

LRMS: (ESI) *m/z* 410.1 $[M+Na]^+$.

FTIR (neat): 3341, 2362, 1701, 1455, 1362, 1247, 1038, 753 cm^{-1}.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1.5
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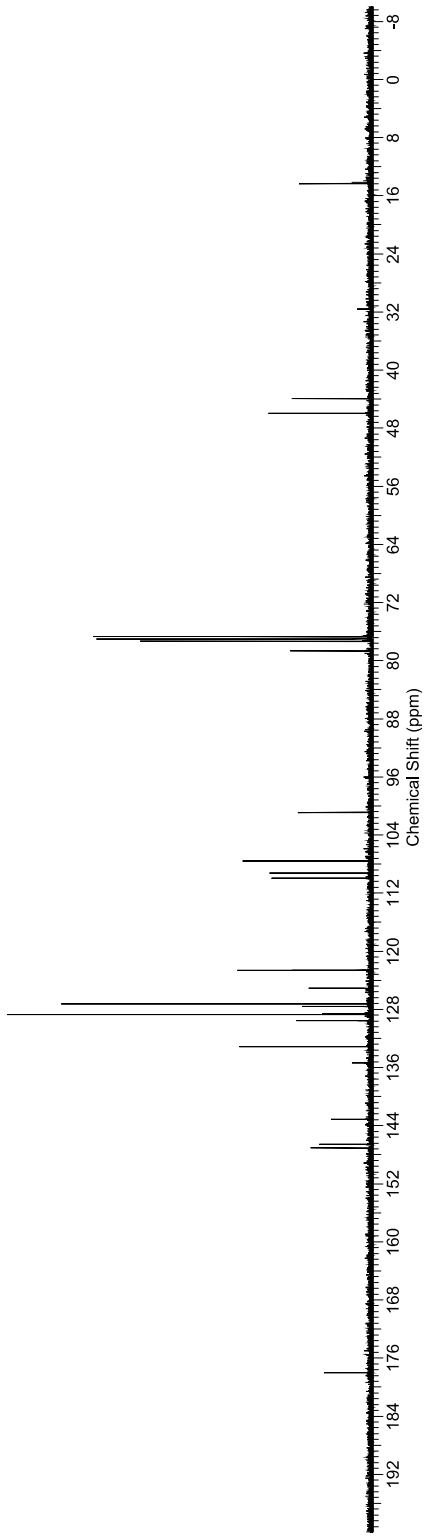
0.5
0
Chemical Shift (ppm)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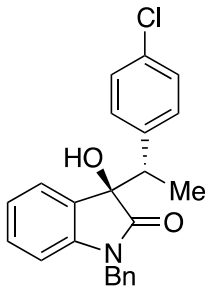
48
56
64
72
80
88
96
104
112
120
128
136
144
152
160
168
176
184
192
Chemical Shift (ppm)

(3*R)-1-Benzyl-3-[(1*S**)-1-(4-chlorophenyl)ethyl]-3-hydroxyindolin-2-one (2.3n)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 4-Chlorostyrene (**2.2n**) (143 μL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3n**) (93 mg, 0.25 mmol, 82%) as a colorless solid.

TLC (SiO_2): R_f = 0.28 (hexanes:ethyl acetate = 2:1).

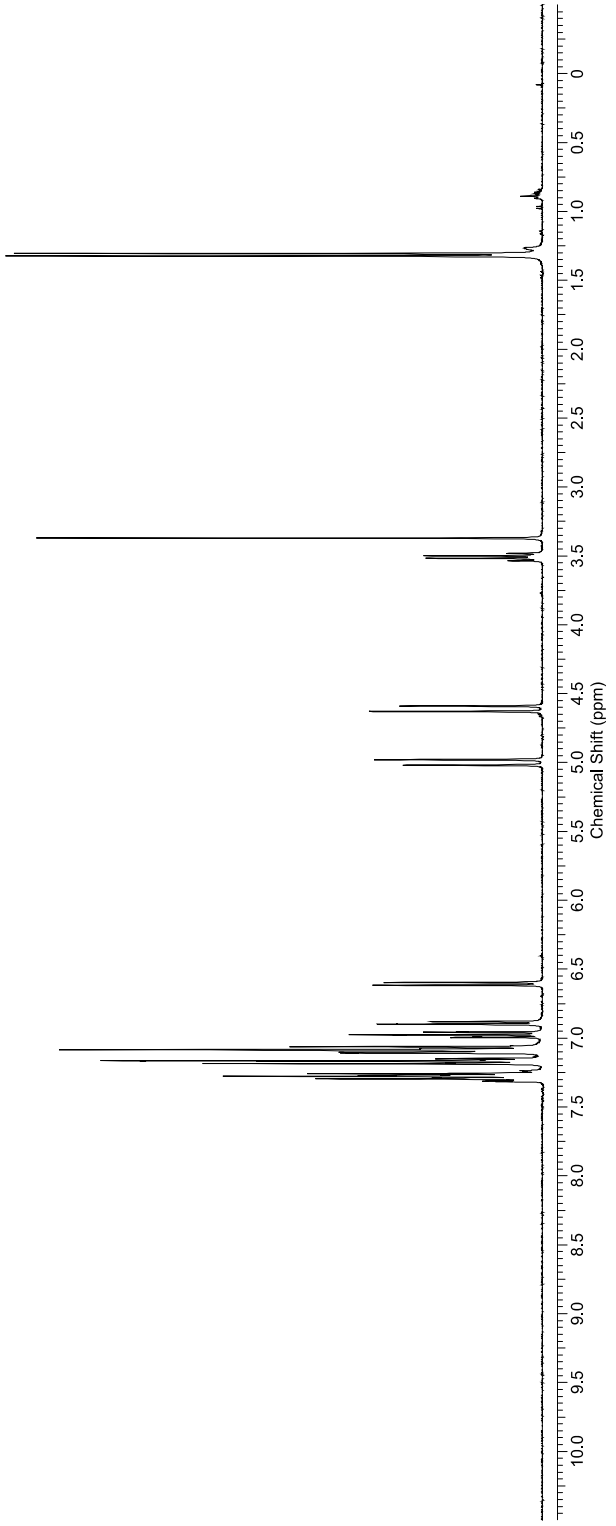
m.p.; 151-153 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.27 (m, 3H), 7.20 - 7.16 (m, 3H), 7.11 - 7.06 (m, 4H), 6.99 (dd, *J* = 8.4, 7.4 Hz, 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.01 (d, *J* = 15.7 Hz, 1H), 4.62 (d, *J* = 15.7 Hz, 1H), 3.51 (q, *J* = 7.2 Hz, 1H), 3.14 (s, 1H), 1.33 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 143.0, 137.8, 135.2, 132.9, 130.7, 129.8, 128.8, 128.4, 127.9, 127.7, 127.2, 124.9, 122.7, 109.3, 78.5, 45.8, 43.9, 13.8.

LRMS (ESI) *m/z* 400.1 $[M+Na]^+$.

FTIR (neat): 3395, 2915, 1698, 1613, 1490, 1363, 1173, 1092, 1012, 908, 826, 727 cm^{-1}.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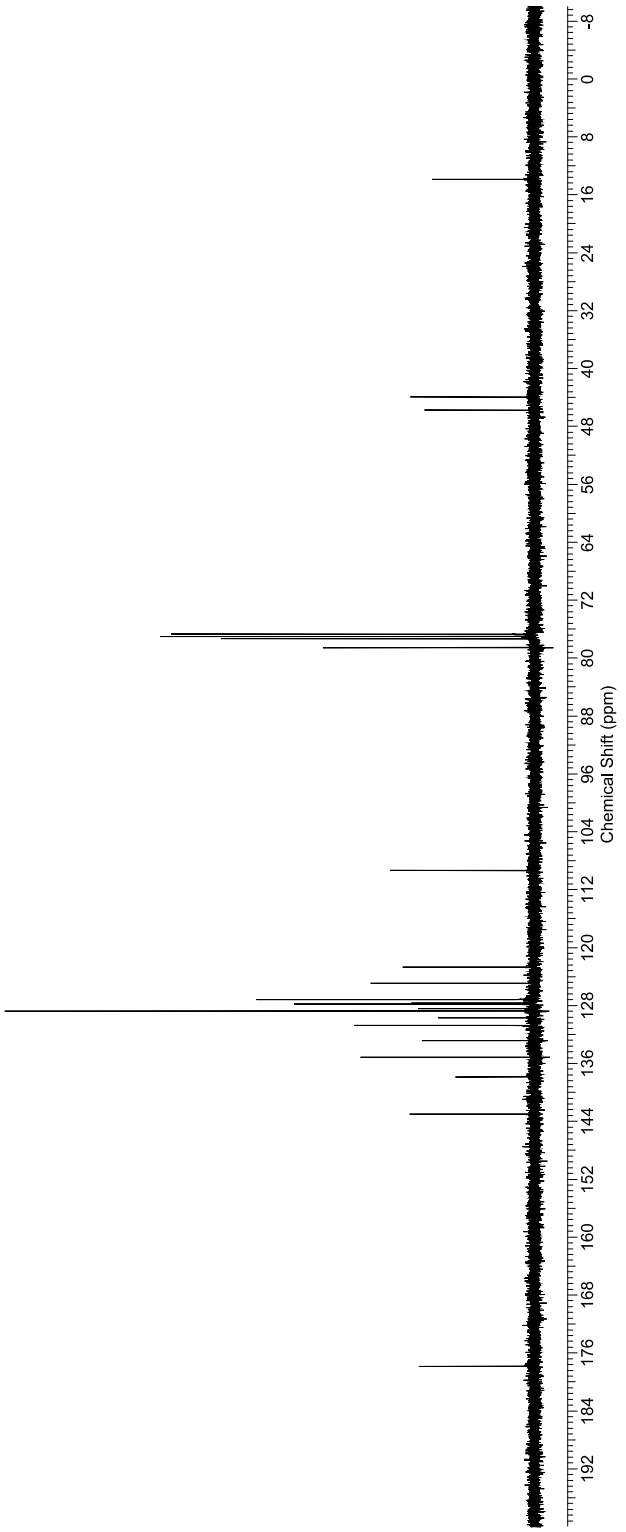
Chemical Shift (ppm)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56
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72
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104
112
120
128
136
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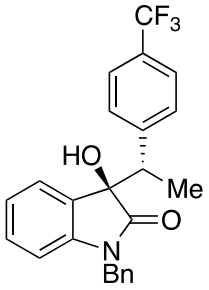
152
160
168
176
184
192
Chemical Shift (ppm)

(3*R)-1-Benzyl-3-hydroxy-3-[(1*S**)-1-(4-(trifluoromethyl)phenyl)ethyl]-indolin-2-one (2.3o)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 1-(trifluoromethyl)-4-vinylbenzene (**2.2o**) (177 µL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated to 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2.5:1) afforded the title compound (**2.3o**) (100 mg, 0.24 mmol, 81%) as a colorless solid.

TLC (SiO_2): R_f = 0.5 (hexanes:ethyl acetate = 1:1).

m.p.: 132-134ºC

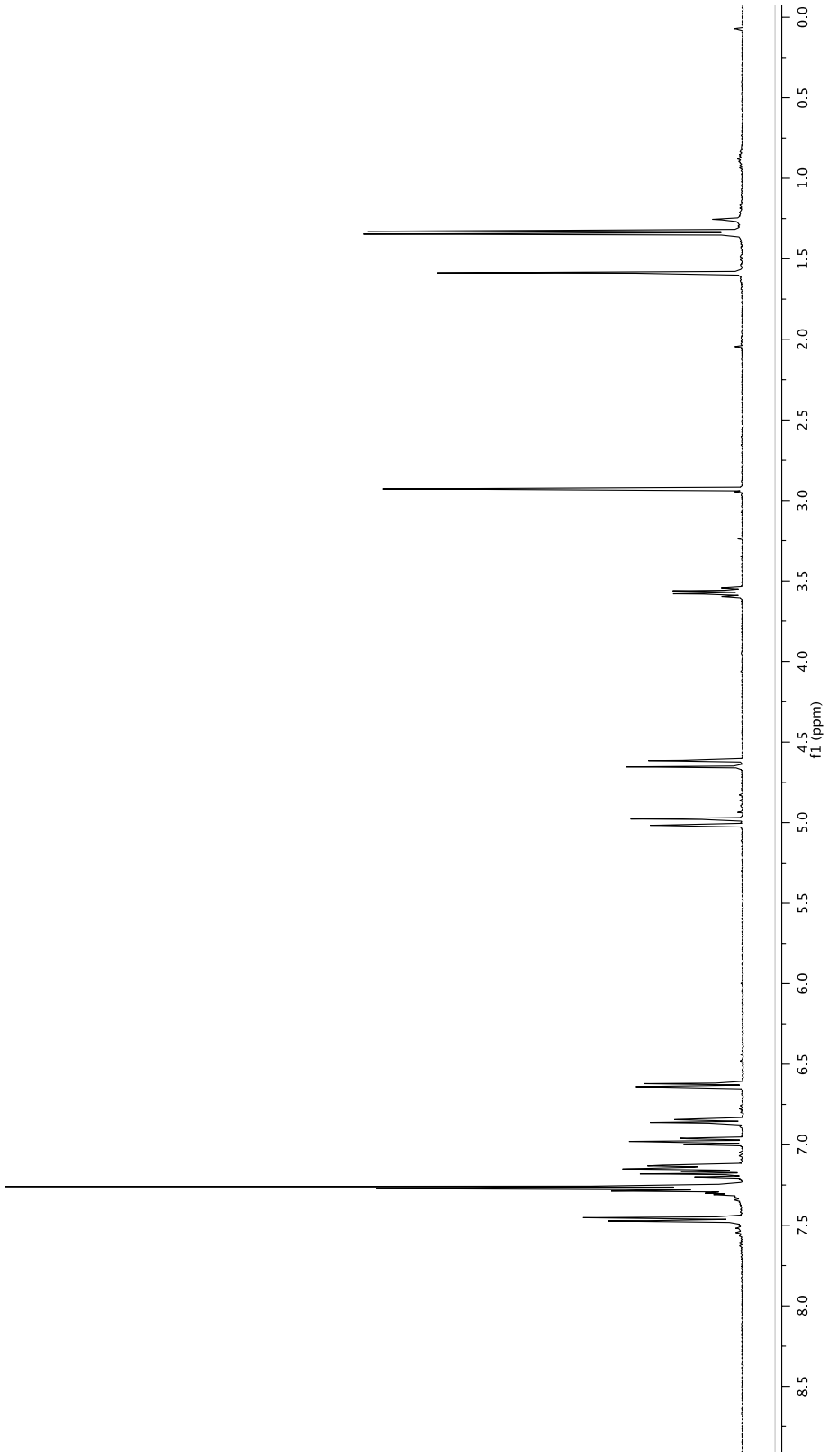
^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.29 - 7.24 (m, 5H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.14 (m, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.63 (d, *J* = 15.7 Hz, 1H), 3.57 (q, *J* = 7.3 Hz, 1H), 2.82 (s, 1H), 1.34 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 177.6, 143.5, 143.0, 135.2, 129.9, 129.8, 129.2 (q, *J* = 32 Hz), 128.8, 128.1, 127.7, 127.2, 124.9, 124.5 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272 Hz), 122.7, 109.4, 78.4, 46.3, 44.0, 13.8.

^{19}F NMR: (376 MHz, $CDCl_3$): δ -62.7.

LRMS: (ESI) *m/z* 434.1 $[M+Na]^+$.

FTIR: (neat): 3397, 2973, 1697, 1491, 1419, 1324, 1119, 1041, 952, 755 cm^{-1}.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3.5
3.0
2.5
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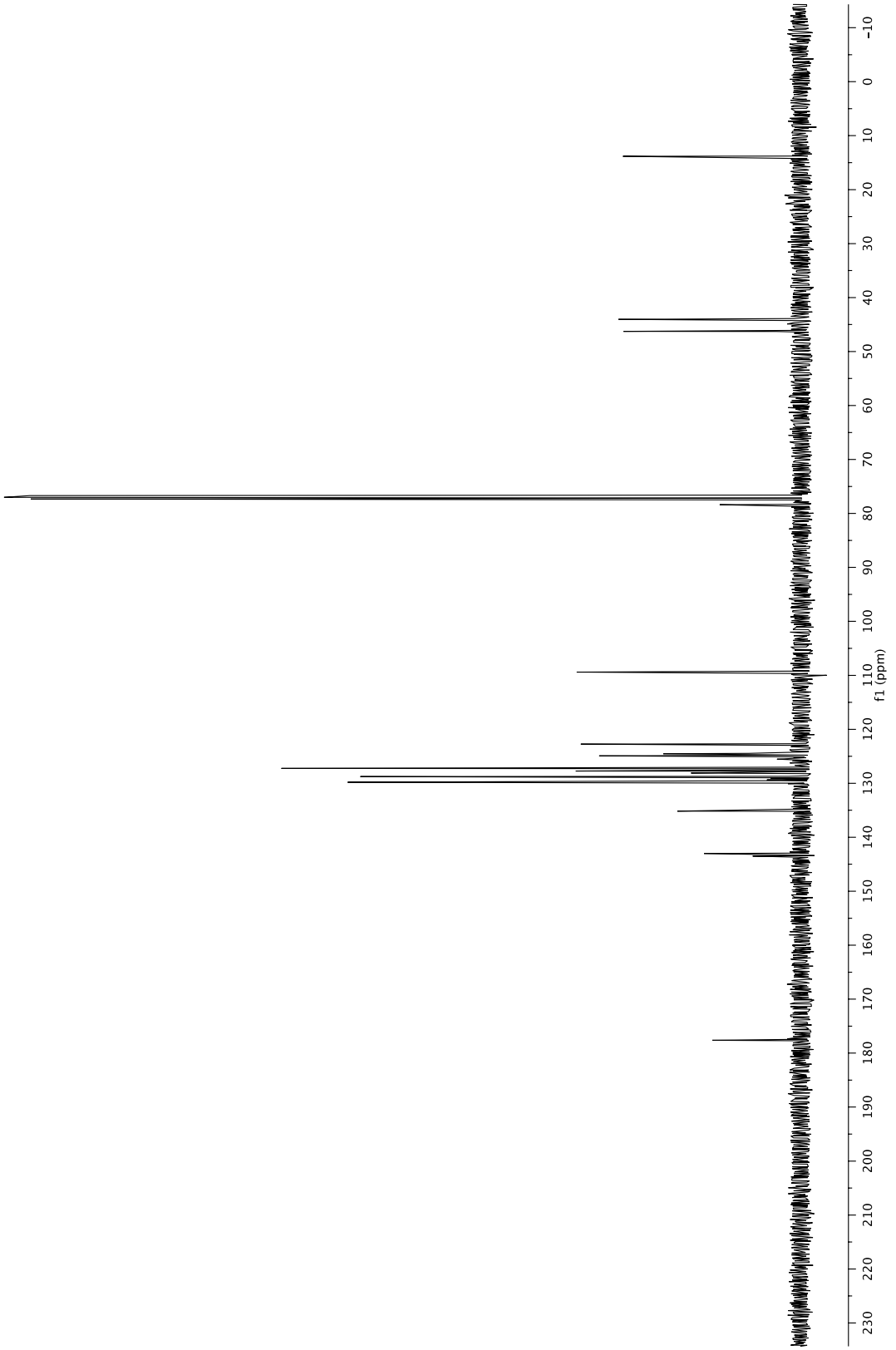
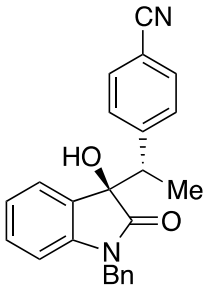
1.5
1.0
0.5
0.0
f1 (ppm)


f1 (ppm)

4-[(*S)-1-((*R**)-1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)ethyl]benzonitrile (2.3p)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 4-Cyanostyrene (**2.2p**) (155 mg, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (r.r (branched:linear) = 8.5:1, d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3p**) (76 mg, 0.21 mmol, 69%) and the linear isomer 1-benzyl-3-hydroxy-3-(4-cyanophenethyl)indolin-2-one (9 mg, 0.03 mmol, 8%) as colorless solid in 76% overall yield.

TLC (SiO_2): R_f = 0.25 (hexanes:ethyl acetate = 2:1).

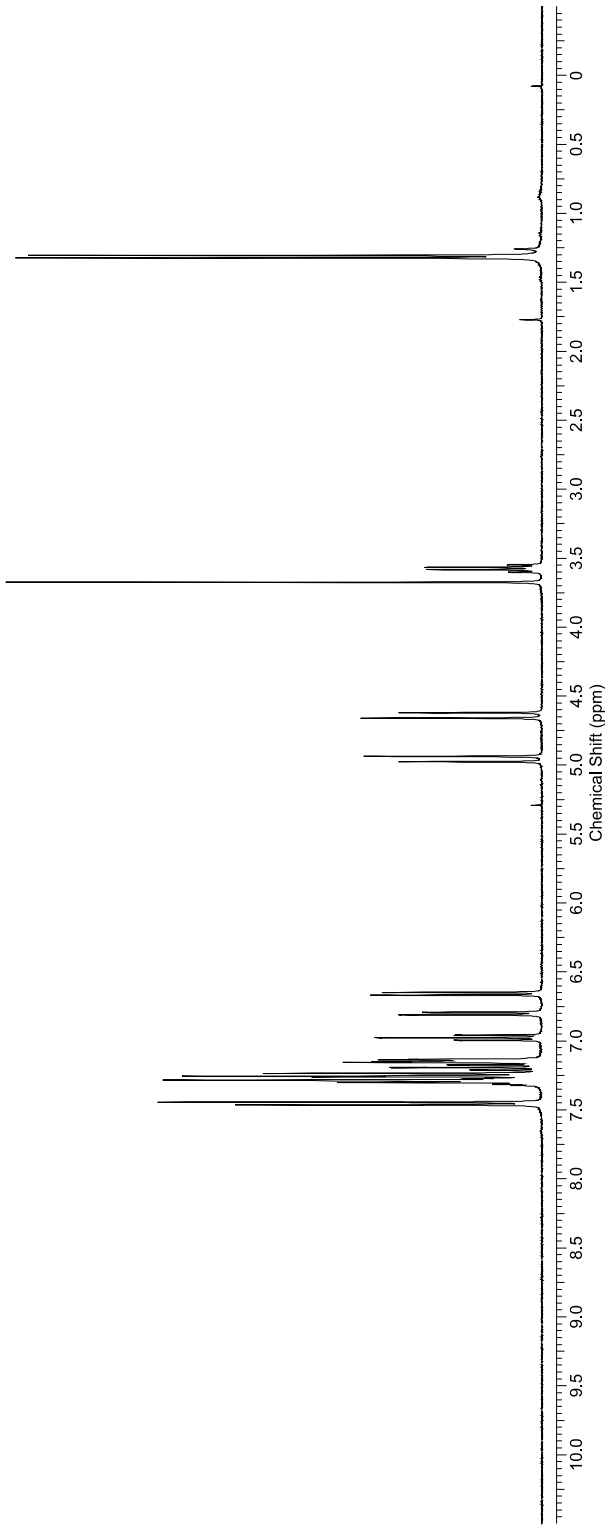
m.p.; 117-119 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.30 - 7.13 (m, 8H), 6.98 (dd, *J* = 7.8, 6.8 Hz, 1H), 6.80 (d, *J* = 6.8 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.64 (d, *J* = 15.7 Hz, 1H), 3.67 (s, 1H), 3.57 (q, *J* = 7.0 Hz, 1H), 1.31 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 145.1, 142.9, 135.1, 131.3, 130.2, 130.0, 128.8, 128.0, 127.9, 127.3, 124.9, 122.9, 118.9, 110.8, 109.4, 78.5, 46.5, 44.0, 13.6.

LRMS (ESI) *m/z* 391.1 $[M+Na]^+$.

FTIR (neat): 2986, 2360, 2227, 1692, 16131, 1486, 1277, 750 cm^{-1}.


Chemical Shift (ppm)
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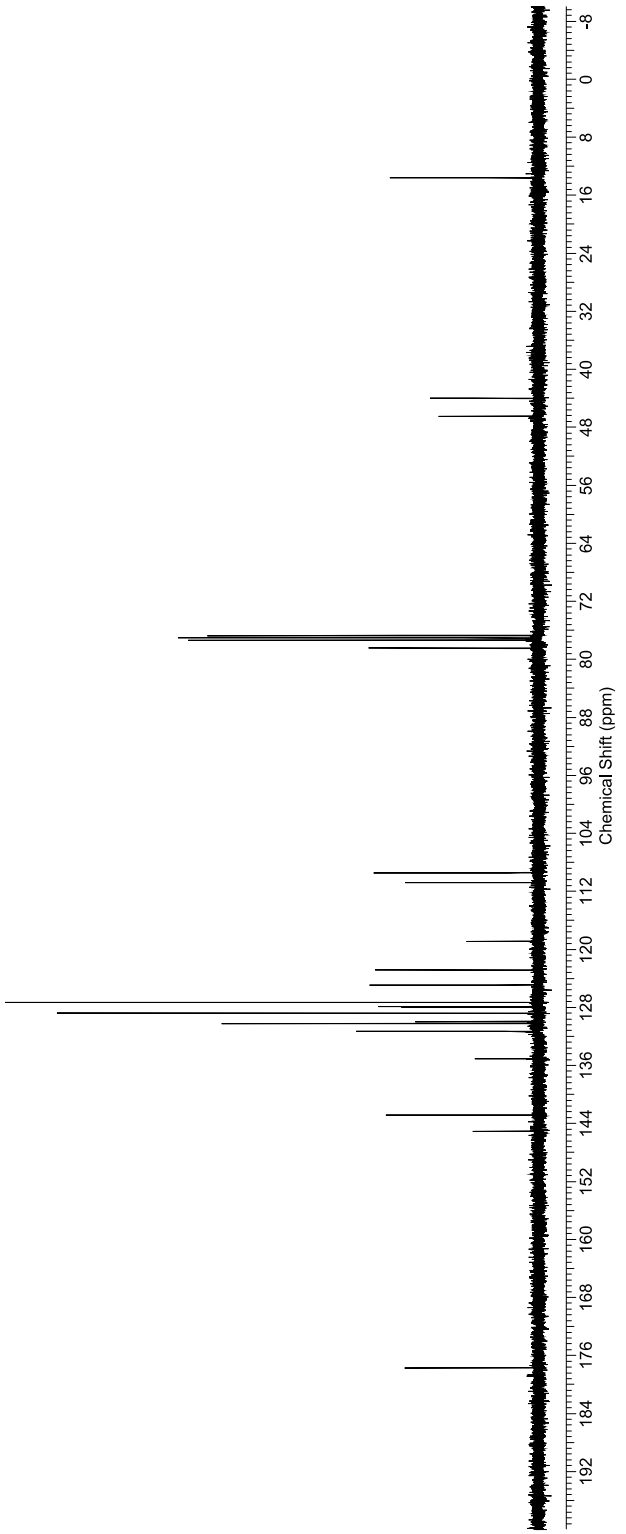
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120
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144
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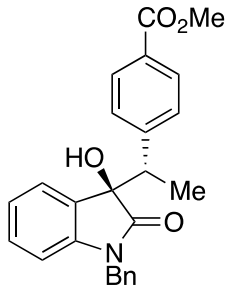
168
176
184
192
Chemical Shift (ppm)

Methyl 4-[(*S)-1-((*R**)-1-benzyl-3-hydroxy-2-oxoindolin-3-yl)ethyl]benzoate (2.3q)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. Methyl-4-vinyl benzoate (**2.2q**) (195 mg, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated to 120 °C (oil bath temperature) for 24 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (r.r (branched:linear) = 4:1, d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2.5:1) afforded the title compound (**2.3q**) (84 mg, 0.21 mmol, 70%) as a colorless viscous oil and the linear isomer methyl-4-{2-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)ethyl}benzoate (20 mg, 0.05 mmol, 17%) as a a colorless viscous oil in 87% overall yield.

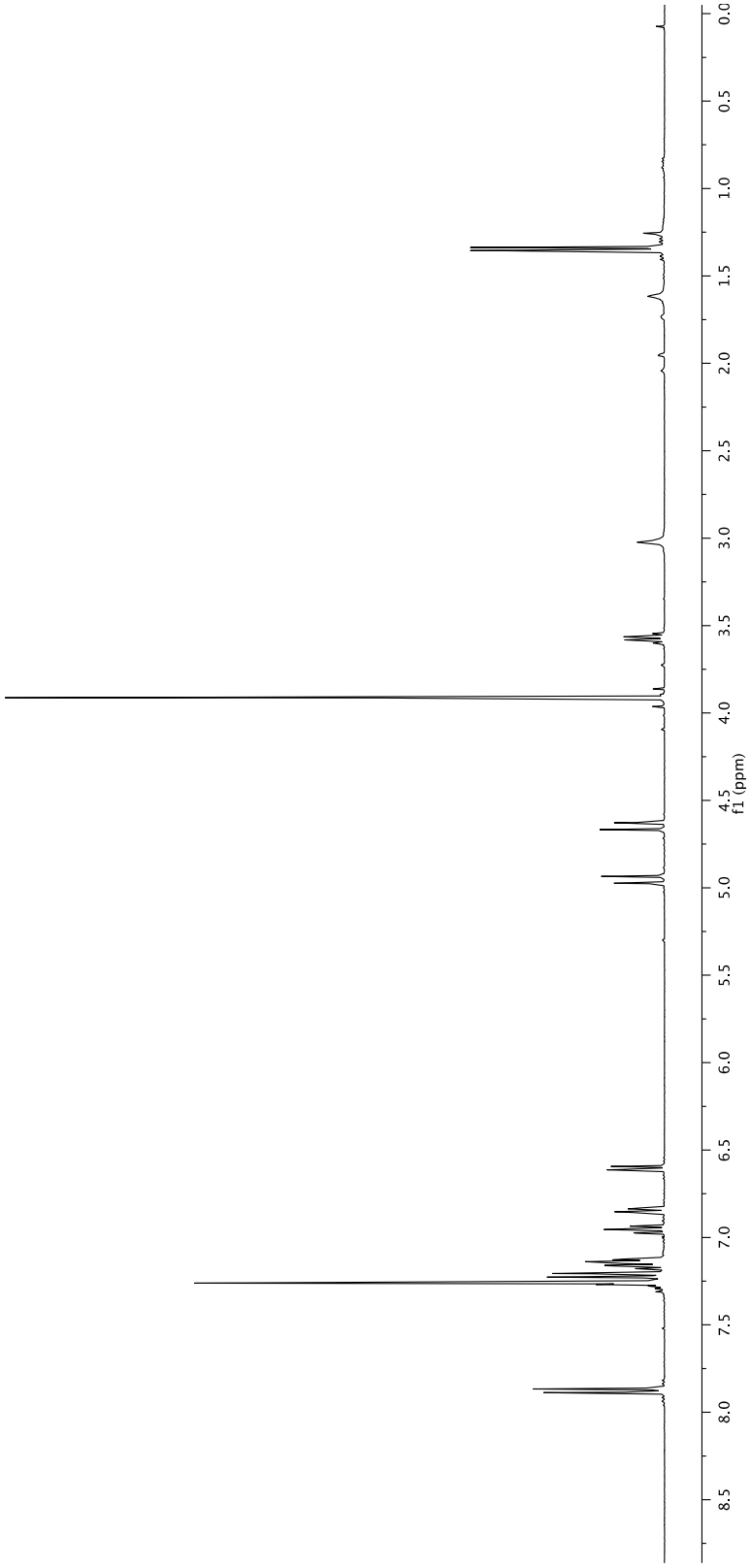
TLC (SiO_2): R_f = 0.38 (hexanes:ethyl acetate = 1:1).

^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.27 - 7.25 (m, 3H), 7.22 (d, *J* = 8.2 Hz, 2H), 7.19 - 7.12 (m, 3H), 6.95 (dt, *J* = 7.6, 0.9 Hz, 1H), 6.83 (dd, *J* = 7.4, 0.8 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.65 (d, *J* = 15.7 Hz, 1H), 3.91 (s, 3H), 3.58 (q, *J* = 7.1 Hz, 1H), 3.21 (br. s, 1H), 1.34 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR: (100 MHz, $CDCl_3$): δ 177.7, 167.0, 144.8, 143.0, 135.2, 129.8, 129.5, 128.9, 128.8, 128.7, 128.2, 127.7, 127.3, 125.0, 122.7, 109.3, 78.5, 52.1, 46.5, 44.0, 13.8.

LRMS: (ESI) *m/z* 424.2 $[M+Na]^+$.

FTIR: (neat): 3340, 2949, 1713, 1701, 1611, 1467, 1364, 1111, 912, 714cm^{-1}.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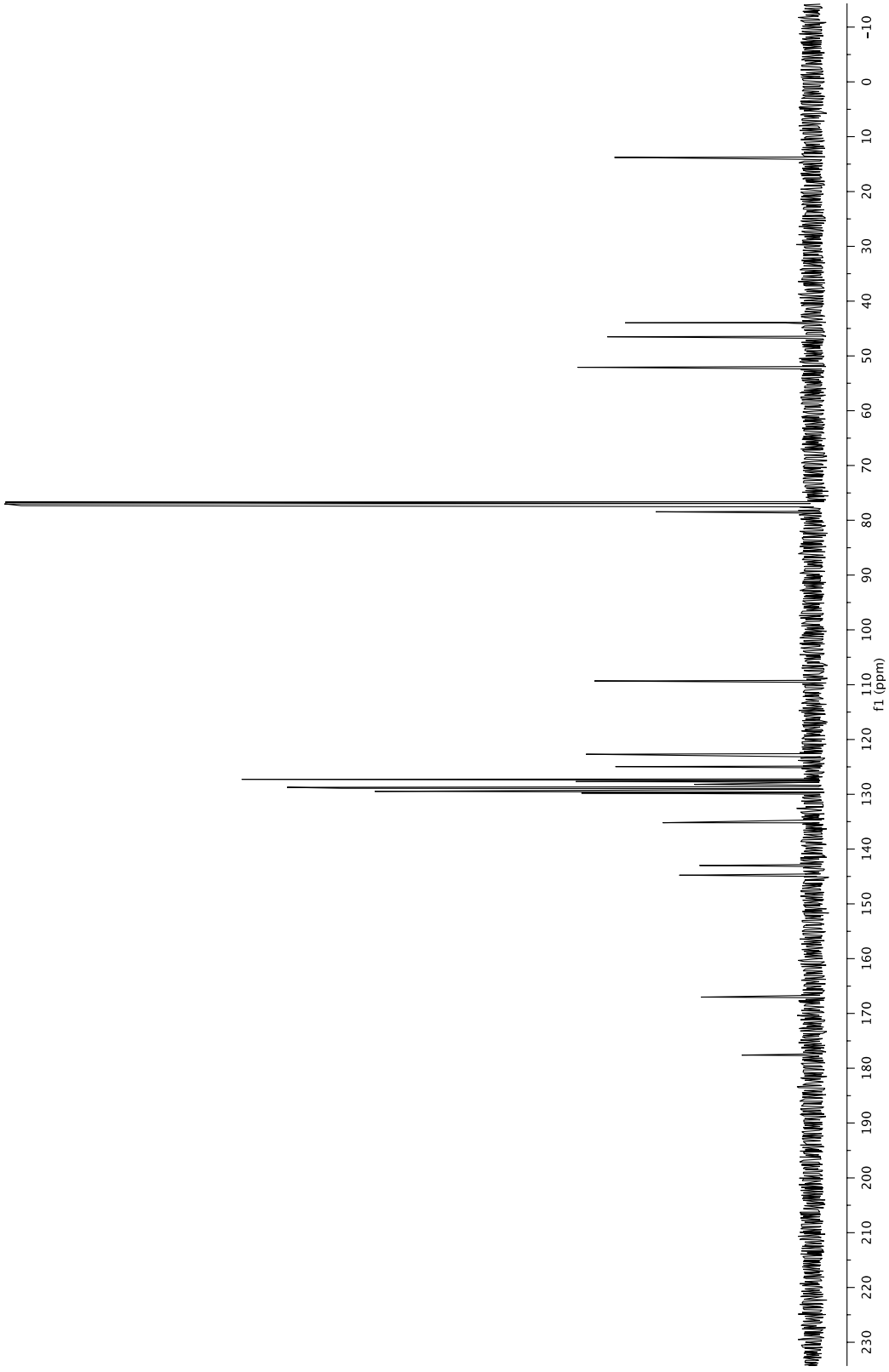
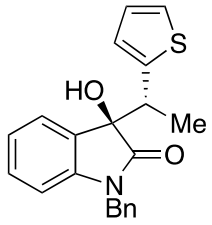

f1 (ppm)

(1*R)-1-Benzyl-3-hydroxy-3-[(3*R**)-1-(thiophen-2-yl)ethyl]indolin-2-one** (**2.3r**)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 1-benzyl-3-hydroxyindolin-2-one (**2.1a**) (72 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with argon. 2-Vinylthiophene (**2.2r**) (128 μL, 1.2 mmol, 400 mol%) and *m*-xylene (0.30 mL, 1.0 M concentration with respect to **2.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 120 °C (oil bath temperature) for 24 hrs, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = >20:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; hexanes:ethyl acetate = 2:1) afforded the title compound (**2.3r**) (91 mg, 0.26 mmol, 87%) as a colorless solid.

TLC (SiO_2): R_f = 0.31 (hexanes:ethyl acetate = 2:1).

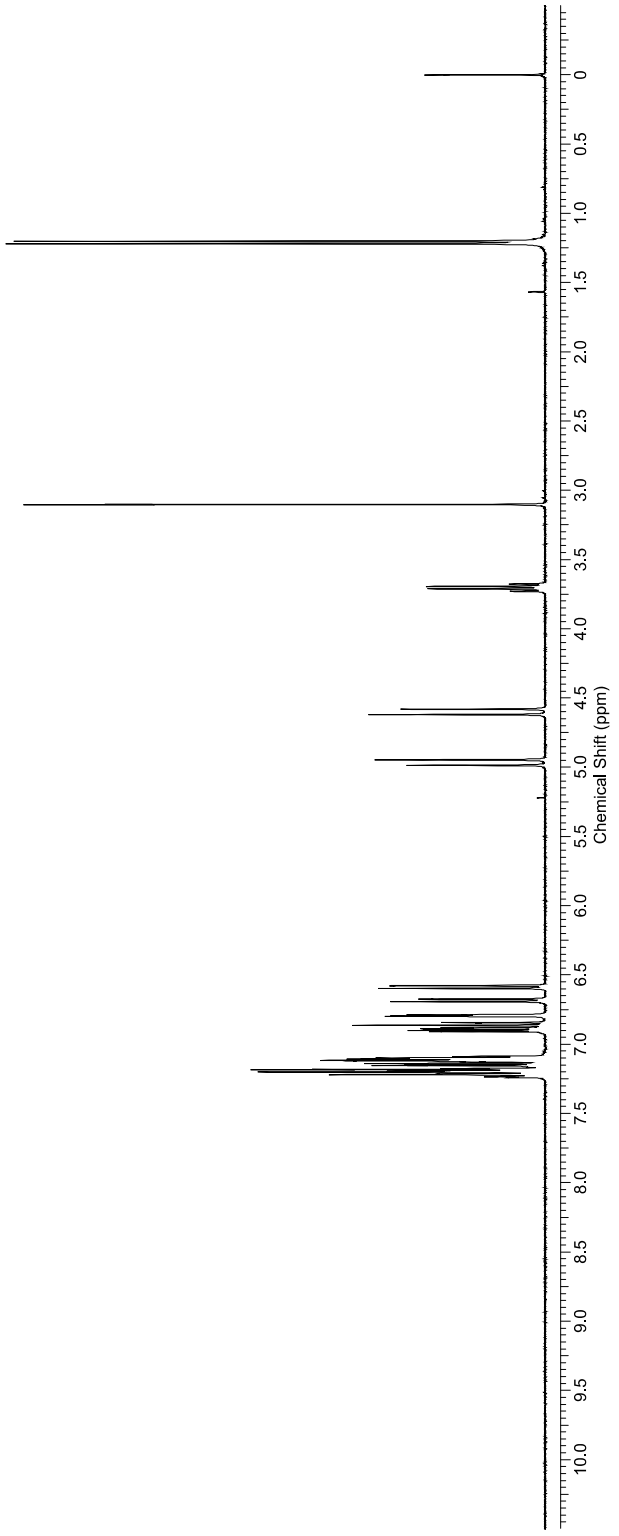
m.p.; 129-130 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 - 7.17 (m, 7H), 6.99 (dd, *J* = 4.5, 3.5 Hz, 1H), 6.95 (dd, *J* = 8.4, 7.4 Hz, 1H), 6.88 (d, *J* = 3.5 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 15.9 Hz, 1H), 4,69 (d, *J* = 15.9 Hz, 1H), 3.78 (q, *J* = 7.2 Hz, 1H), 3.14 (br. s, 1H), 1.30 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 143.3, 142.5, 135.3, 129.8, 128.8, 127.9, 127.7, 127.3, 126.3, 126.2, 125.0, 124.6, 122.8, 109.3, 78.3, 44.0, 42.1, 15.2.

LRMS (ESI) *m/z* 372.1 $[M+Na]^+$.

FTIR (neat): 3390, 2971, 1698, 1613, 1466, 1370, 1174, 731, 699 cm^{-1}.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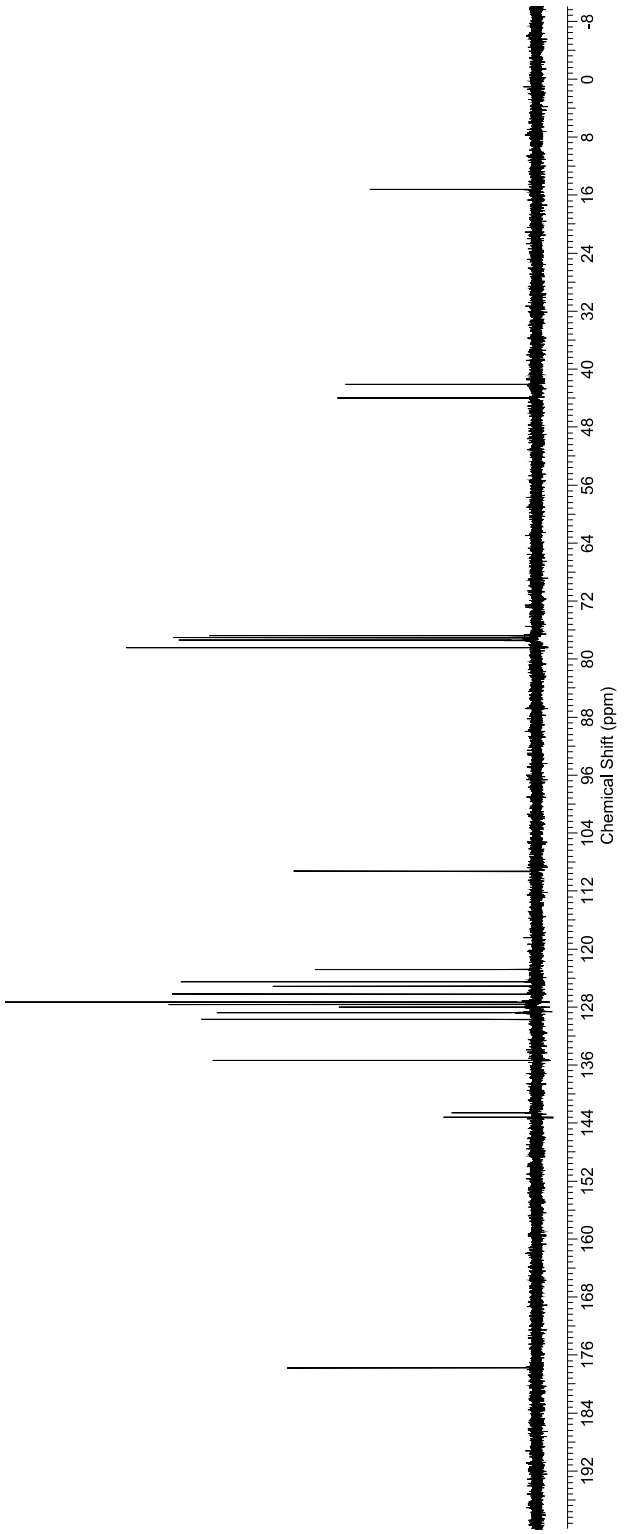
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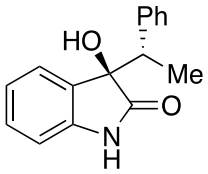
Chemical Shift (ppm)

(3*R)-3-Hydroxy-3-((1*S**)-1-phenylethyl)indolin-2-one** (**2.3s**)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Ru_3(CO)_{12}$ (3.8 mg, 6.0 x 10^{-3} mmol, 2 mol%), tricyclohexylphosphine (10.1 mg, 3.6 x 10^{-2} mmol, 12 mol%), 1-adamantanecarboxylic acid (5.4 mg, 3.0 x 10^{-2} mmol, 10 mol%) and 3-hydroxyindolin-2-one (**1b**) (45 mg, 0.3 mmol). The tube was sealed with a rubber septum and purged with nitrogen. Styrene (**2.2g**) 158 μL, 0.9 mmol, 400 mol%) and chlorobenzene (0.30 mL, 1.0 M concentration with respect to **2.1b**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated to 120 °C (oil bath temperature) for 72 h, at which point the reaction mixture was allowed to cool to ambient temperature and concentrated *in vacuo* to afford the crude hydroxyoxindole (d.r. = 15:1 as determined by ^{1}H NMR spectroscopy). Purification of the crude product by flash column chromatography (SiO_2; dichloromethane:diethyl ether = 5:1) afforded the title compound (**2.3s**) (55 mg, 0.25 mmol, 72%) as a white solid.

TLC (SiO_2): R_f = 0.20 (dichloromethane:diethyl ether = 5:1).

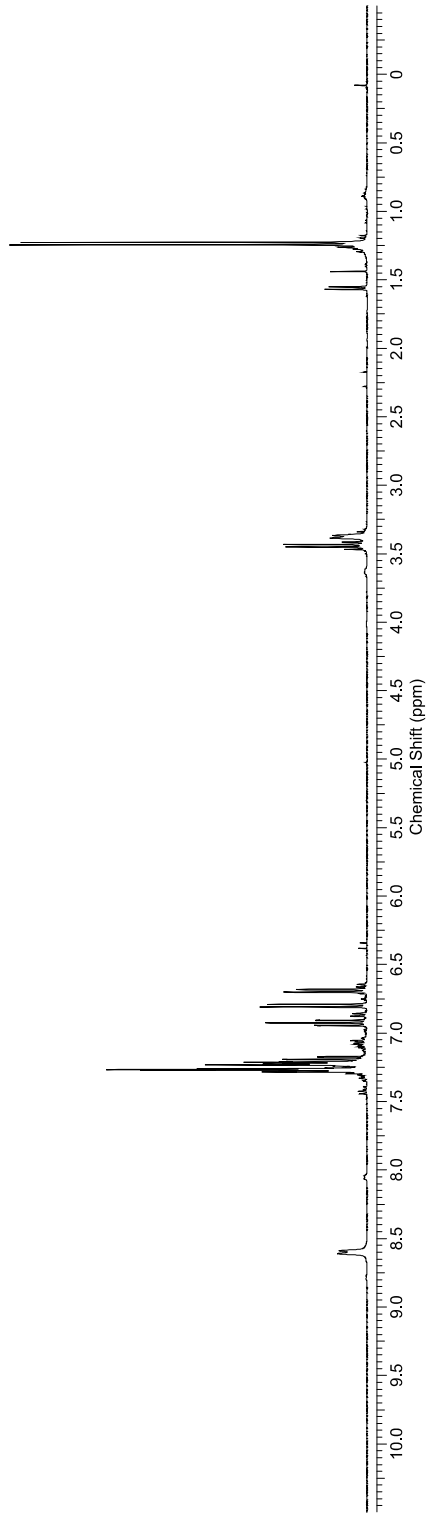
m.p.: 98-100 ºC

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (br. s, 1H), 7.30 - 7.21 (m, 5H), 7.19 (dd, *J* = 7.8, 7.0 Hz, 1H), 6.93 (dd, *J* = 7.4, 7.0 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.4, 1H), 3.44 (q, *J* = 7.0 Hz, 1H), 3.38 (br. s, 1H), 1.23 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6, 140.9, 139.1, 129.6, 129.6, 128.6, 127.7, 127.2, 125.7, 122.4, 110.1, 79.3, 45.9, 13.9.

LRMS (ESI) *m/z* 276.10 $[M+]^+$.

FTIR (neat): 3271, 2359, 1621, 1471, 1206, 1183, 907, 754 cm^{-1}.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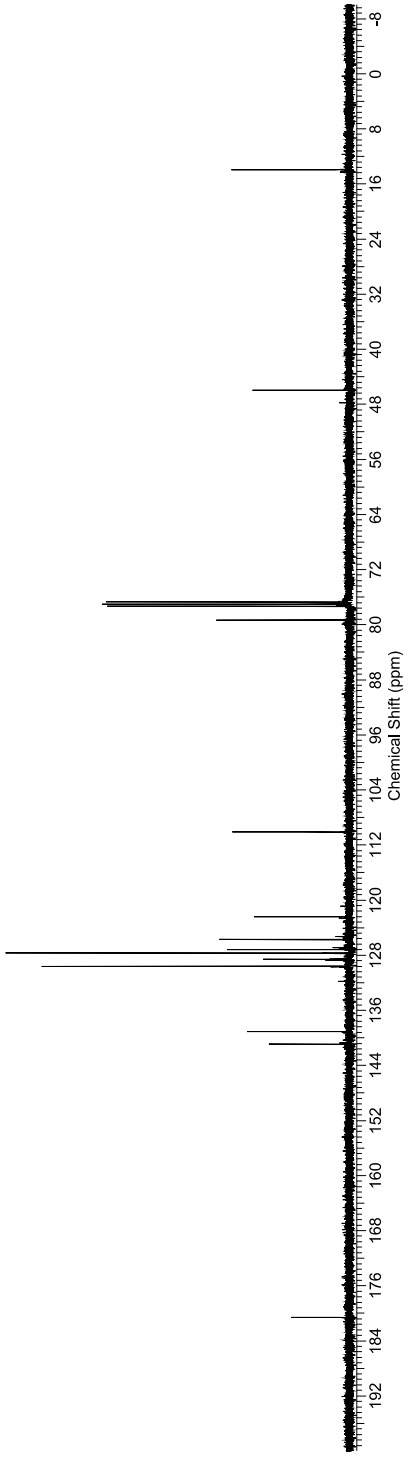
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Chemical Shift (ppm)

Chapter 3: Osmium Catalyzed C-C Coupling of α-Olefins to Diols, Ketols or Hydroxy Esters

3.1 Background

The discovery of alternate classes of catalytic C-C couplings that convert α-olefins to value-added products remains an important goal.[1] In connection with the development of C-C bond forming reactions beyond hydroformylation *via* transfer hydrogenation, the Krische group discovered that by using a ruthenium catalyst modified by phosphine ligands catalyze the coupling of vicinally deoxygenated hydrocarbons with a variety of π-unsaturates including dienes,[40] acrylates[50] and alkynes.[51] Krische and co-workers also report that with the use of a Ru_3CO_{12} catalyst modified by PCy_3 one can transform α-olefins to *N*-benzyl-3-hydroxy-2-oxindoles to form product of hydrohydroxyalkylation with excellent control for the branch isomer, as well as the *anti*-diastereomer.[28] However, this chemical transformation was restricted solely to *N*-benzyl-3-hydroxy-2-oxindoles. This limitation could be attributed for the exceptional reactivity of the transient isatin formed *in-situ*. The ongoing efforts have now lead to the discovery of osmium (0) catalyst allowing for the C-C coupling of α-olefins and higher order α-olefins with a wider range of electrophiles such as 1,2-diols, α-ketols and α-hydroxy esters.[29]

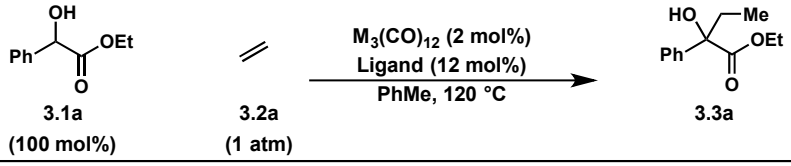
3.2 Reaction Development

The limitation with the ruthenium (0) catalyzed C-C coupling of α-olefins to *N*-benzyl-3-hydroxy-2-oxindoles were believed to stem from the high energetic barrier to oxidative coupling. With Hoffmann's analysis of conversion of metal bisolefin complexes to metallacyclopentanes and along with experimental evidence from the Krische group, the oxidative coupling should be proportional to the degree of backbonding in the preceding

metal-olefin π-complex.[41,52] Backbonding confers nucleophilic character to the bound olefins and can be viewed as an oxidative addition to the C-C double bond of the π-bond to form a metallacyclopropane. An example can be viewed in the Kulinkovich reaction where the titanium(II)-olefin complexes behave as vicinal dianions.[48] The hypothesis now was that by utilizing a more strongly reducing metal could facilitate oxidative coupling of α-olefins to less reactive electrophiles and allow a broader substrate scope to participate in transfer hydrogenative C-C couplings.

Carbonyl stretching frequencies of isostructural ruthenium and osmium complexes $HClM(CO)(PPh_3)_3$, yielded ruthenium with a stretching frequency of 1922 cm^{-1} and osmium with 1906 cm^{-1}.[53] These frequencies suggest that osmium is a stronger π-donor than ruthenium. For this reason, osmium (0) complexes were assayed in the coupling of ethyl mandelate with ethylene gas (**Table 3.1**). It was found that with triaryl phosphine ligands were ineffective, but with the use of tricyclohexylphosphine with $Os_3(CO)_{12}$ provided the desired coupling product in 57% yield **3.3a**. Given this promising result, the use of Buchwald type ligands proved to be the best suited for the transformation and with the use of XPhos the product **3.3a** was obtained in 78% yield. Notably, the use of the corresponding ruthenium (0) catalysts was unable to promote the described reaction.

Table 3.1: Selected examples for the catalytic system optimization between ethyl mandelate and ethylene



Entry	Metal	Ligand	Yield
1	Ru	PCy_3	-
2	Ru	XPhos	-
3	Os	PCy_3	57
4	Os	CyJohnPhos	31
5	Os	RuPhos	60
6	Os	Xphos	78

3.3 PROPOSED MECHANISM

It is unclear whether the catalyst is a mononuclear or dimetallic or even trimetallic. Upon heating toluene solutions of $Os_3(CO)_{12}$ with XPhos in the presence and absence of adamantane carboxylic acid, crystals of the dinuclear complex $Os_2(CO)_4(O_2CR)_2(XPhos)_2$ (**Figure 3.1**) and the trinuclear complex $Os_3(CO)_{11}(XPhos)$ (**Figure 3.2**)[54], respectively, were isolated and characterized by X-ray diffraction.

Figure 3.1: Crystal structure of $Os_2(CO)_4(O_2CR)_2(XPhos)_2$

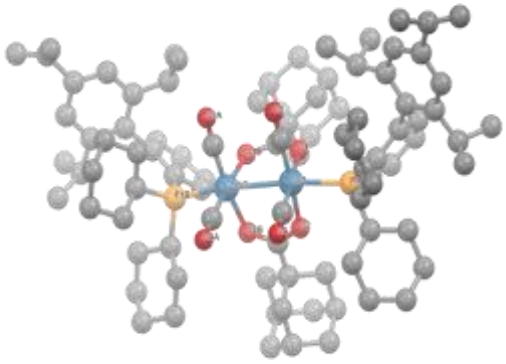
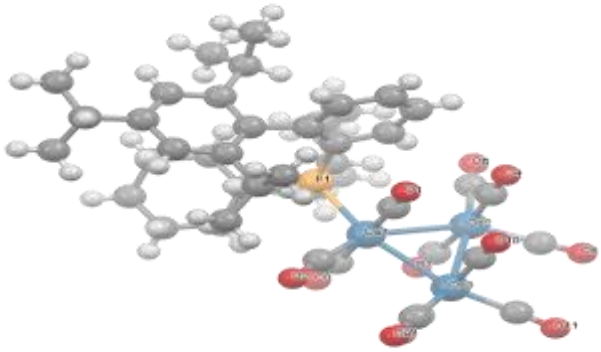


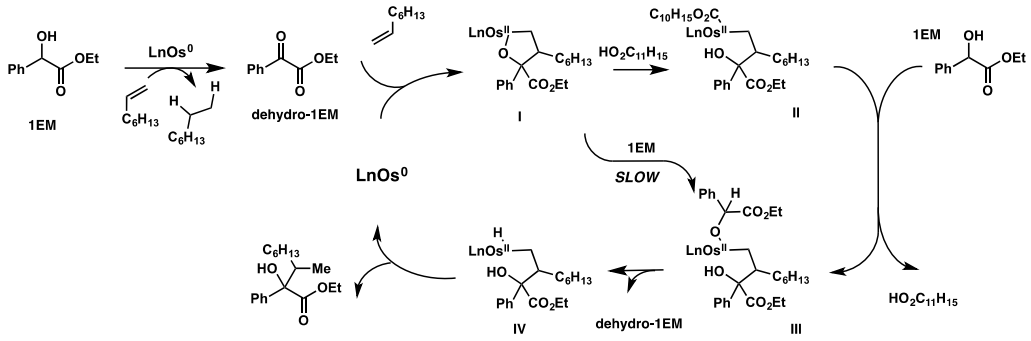
Figure 3.2: Crystal structure of $Os_3(CO)_{11}(XPhos)$



A plausible mechanism has been proposed (**Figure 3.3**). Oxidative coupling of **dehydro-1EM** with 1-octene provides the oxaosmacycle **I**.[6] The oxo-ester **dehydro-1EM** may be generated *via* alcohol dehydrogenation.[55] Direct protonation of the oxaosmacycle by a molecule of ethyl mandelate **1EM** would form the osmium alkoxide **III**. This cleavage of

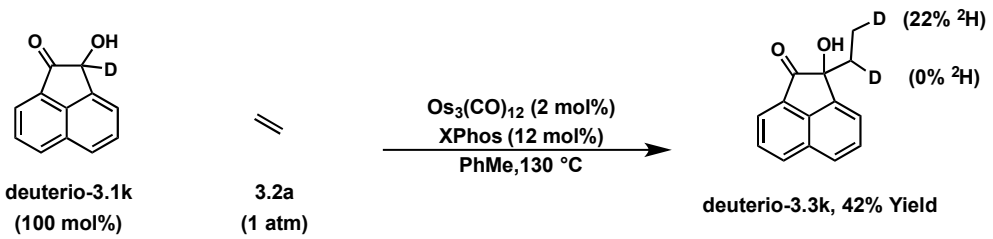
the oxaosmacycle would require a 4-membered transition state and is postulated to be slow compared to the cleavage of the oxaosmacycle by the 1-adamantanecarboxylic acid which proceed *via* 6-membered transition state.[41] Cleavage by 1-adamantanecarboxylic acid of the oxaosmacycle would provide the osmium alkoxide **II** which could then undergo a ligand exchange with another molecule of ethyl mandelate leading to the same osmium alkoxide species **III**. At the stage of osmium alkoxide **III** can undergo a β-hydride elimination providing the osmium hydride species **IV** that can undergo a C-H reductive elimination furnish our coupling product and regenerating the osmium (0) catalyst.

Figure 3.3: Proposed catalytic mechanism for ethyl mandelate and 1-octene



To challenge the veracity of the proposed mechanism following isotopic labeling experiment was performed (**Scheme 3.1**). The deuterated acenaphthylene ketol *deuterio*-**3.1k** was exposed to ethylene. Deuterium incorporation occurs exclusively at the methyl group (22% ^{2}H). The transfer of deuterium from the carbinol position of *deuterio*-**3.1k** to the methyl group of *deuterio*-**3.3k** is consistent with the proposed mechanism and low levels of deuterium incorporation may be attributed to exchange with adventitious water.[56]

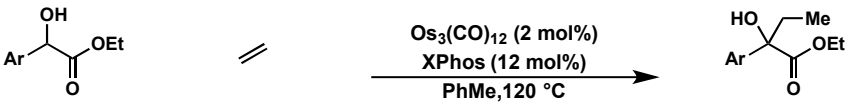
Scheme 3.1: Deuterium labeling experiments with *deuterio*-**3.3k**



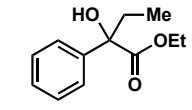
3.4 REACTION SCOPE

With the optimized conditions in hand, aryl and heteroaryl-substituted α-hydroxy esters participated in couplings with ethylene gas to form products of ethylation (**Table 3.2**). The reaction tolerated a variety of functional groups on the aryl ring from halides, electron donating and electron withdrawing groups **3.3b-3.3e**. Heteroaryl rings such as furans and thiofurans also participated in the reaction yielding the desired coupling products in 64 and 70% yield respectively **3.3h** and **3.3i**. One limitation with the α-hydroxy esters was that the reaction did not tolerate substitution at the ortho-position of the reactive site. This may be due to the sterics surrounding the formation of the oxaosmacycle which would potentially disfavor the reaction to proceed.

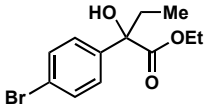
Table 3.2: Coupling of ethylene with ethyl mandelate derivatives



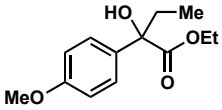
Ar = Ph, 3.1a	Ar = 4-Br-Ph, 3.1b	Ar = 4-MeO-Ph, 3.1c
Ar = 4-CF_3-Ph, 3.1d	Ar = 3-CF_3-Ph, 3.1e	Ar = 5-(benzodioxle), 3.1f
Ar = 4-MeS-Ph, 3.1g	Ar = 2-furyl, 3.1h	Ar = 2-thienyl, 3.1i



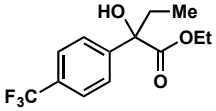
3.3a, 78% Yield



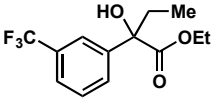
3.3b, 74% Yield



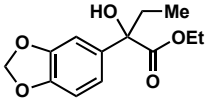
3.3c, 61% Yield



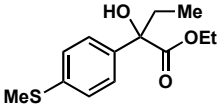
3.3d, 77% Yield



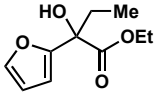
3.3e, 76% Yield



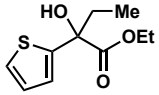
3.3f, 61% Yield



3.3g, 61% Yield



3.3h, 64% Yield

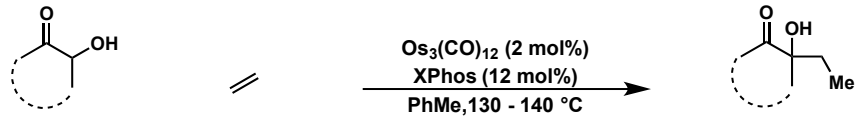


3.3i, 70% Yield

α-Ketols also participated in the coupling with ethylene gas (**Table. 3.3**). Single regioisomers were obtained. Benzofused α-ketols as well as simple aliphatic α-ketols such as α-hydroxycyclohexanone participated smoothly under the optimized reaction conditions. In contrast to the coupling of α-ketols which are redox-neutral transformations, the coupling of 1,2-diols with ethylene gas represent an oxidative process in which 1 equivalent of H_2 is produced and would require a transfer to an acceptor. Initial attempts in coupling ethylene to 1,2-cyclohexane diol and other 1,2-diols lead to only modest yields of the desired coupling

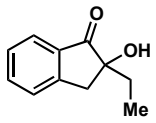
products. To address lost in yield, the use of 1-adamantane carboxylic acid was known to catalyze hydrogenolysis and transfer hydrogenolysis of oxa-metalacycles.[41] To our delight the use of catalytic amounts of the acid improved the couplings of diols to ethylene gas (**Table 3.4**).

Table 3.3: Coupling of ethylene with α-ketol derivatives

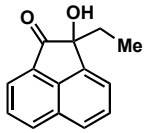


3.1j - 3.1o (100 mol%) | **3.2a** (1 atm) | **3.3j - 3.3o**

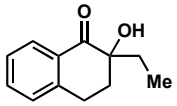
2-OH-indanone, 3.1j	2-OH-acenapthylenone, 3.1k	2-OH-tetralone, 3.1l
3-OH-chromanone, 3.1m	3-OH-2,2-Me_2-chromanone, 3.1n	2-OH-cyclohexanone, 3.1o



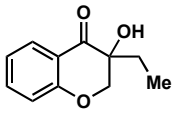
3.3j, 84% Yield



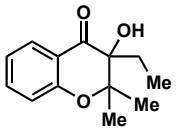
3.3k, 63% Yield



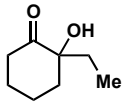
3.3l, 83% Yield



3.3m, 86% Yield

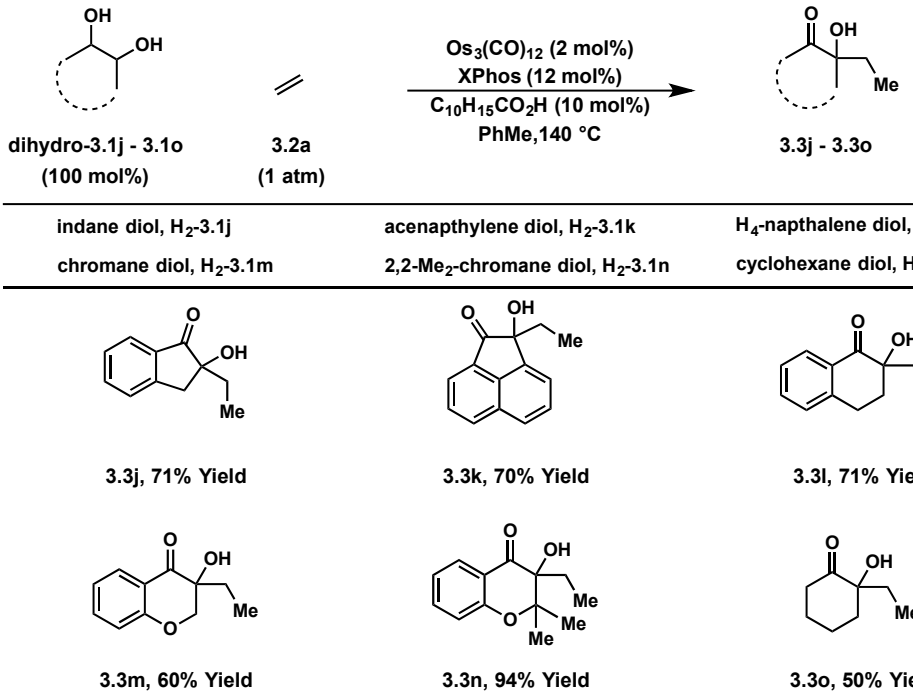


3.3n, 85% Yield



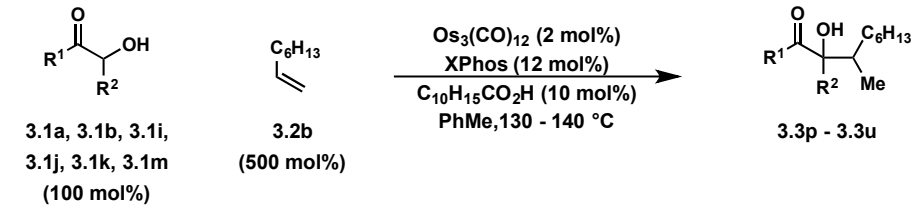
3.3o, 73% Yield

Table 3.4: Coupling of ethylene with 1,2-diol derivatives

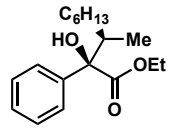


Higher order α-olefins such as 1-octene was used to test the applicability of the reaction to a select handful of α-hydroxy esters, and ketols. Slight modification by running the reaction more concentrated in 1-octene and use of 1-adamantane carboxylic acid resulted good yields of the desired coupling product (**Table 3.5**). The *syn*-diastereomer was obtained in good to poor selectivity. This could be accounted by the high temperatures as well as both coupling partners being acyclic, leading to many configurations the molecules can be in when coming together. The relative stereochemistry was determined by X-ray diffraction analysis of a derivative of **3.3q**.

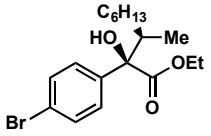
Table 3.5: Coupling of 1-octene with α-hydroxy esters and ketols



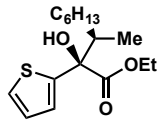
3.1a, 3.1b, 3.1i, 3.1j, 3.1k, 3.1m (100 mol%) | 3.2b (500 mol%) | 3.3p - 3.3u



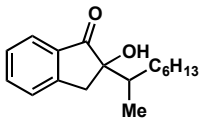
3.3p, 62% Yield, 5:1 dr



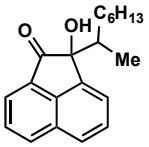
3.3q, 61% Yield, 4:1 dr (X-Ray)



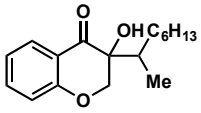
3.3r, 80% Yield, 5:1 dr



3.3s, 85% Yield, 1:1 dr



3.3t, 63% Yield, 1:1 dr

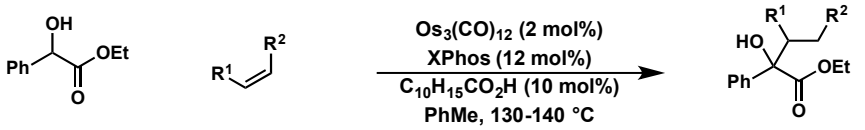


3.3u, 95% Yield, 2:1 dr

Other alkenes were also tested in coupling with ethyl mandelate. The yield was modest but provided a wider variety of alkenes with functional handles (**Table 3.6**). Common alkenes such as allylbenzene and allyl acetate proceeded in the reaction both giving exclusively the branch coupling products. Selectivity for one diastereomer over the other was very low to non-existent.

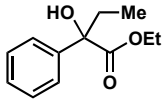
The hydrogenative coupling α-olefins can be conducted in an oxidative, redox-neutral and reductive mode. This unique feature allows the use of this chemistry at any oxidation level. As shown with varying oxidation states of acenaphthenequinone coupling with 1-octene, all providing the product of coupling **3.3t** in excellent to good yields (**Table 3.7**). The unique characteristic of this chemistry allows one to bypass discrete redox manipulations, saving steps.[57]

Table 3.6: Coupling of ethyl mandelate with functionalized olefins

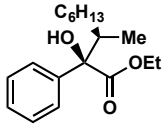


3.1a (100 mol%) | **3.2a - 3.2f** (500 mol%) | **3.3a, 3.3p, 3.3v - 3.3y**

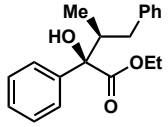
$R^1 = R^2 = H$, 3.2a	$R^1 = H$, $R^2 = C_6H_{13}$, 3.2b	$R^1 = H$, $R^2 = CH_2Ph$, 3.2c
$R^1 = H$, $R^2 = OPiv$, 3.2d	dihydrofuran, 3.2e	$R^1 = H$, $R^2 = CH_2OAc$, 3.2f



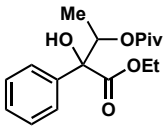
3.3a, 78% Yield



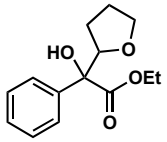
3.3p, 62% Yield, 5:1 dr



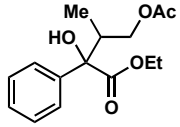
3.3v, 58% Yield, 5:1 dr



3.3w, 84% Yield, 1.5:1 dr

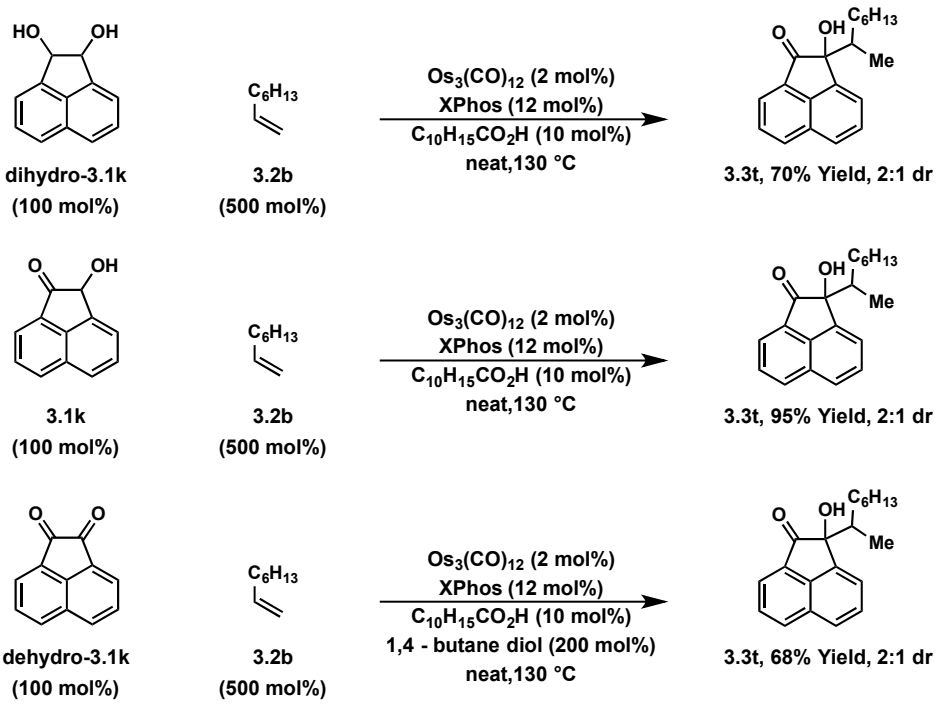


3.3x, 78% Yield, 1:1 dr



3.3y, 60% Yield, 1.6:1 dr

Table 3.7: Coupling of 1-octene with different oxidation states of acenaphthenequinone



3.5 CONCLUSION

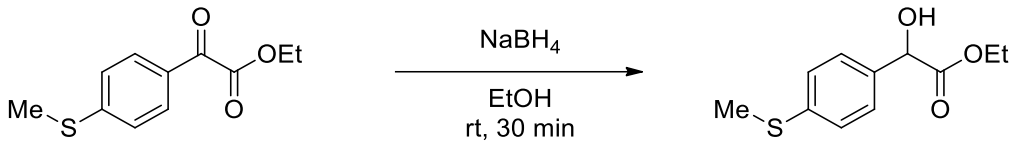
In summary, the technology to be able to transform abundant chemical feedstocks such as α-olefins to value added products has been shown with the absence of stoichiometric byproducts. Not only being limited to α-olefins but higher order olefins were also able to participate in the reaction with the use of the osmium (0) catalyst modified by XPhos.[29] This advancement from the work with *N*-benzyl-3-hydroxy-2-oxindole and α-olefins[28] shows that the development of more advanced catalysts is the key to being able to one day couple abundant chemical feed stocks with primary or secondary aliphatic alcohols in the absence of stoichiometric byproducts.

3.6 Experimental Section

General Information: All reactions were run under an atmosphere of argon. $Os_3(CO)_{12}$, XPhos, 1-adamantanecarboxylic acid, alkenes **3.2a-3.2f**, α-hydroxy ester **3.1a**, α-ketol **3.1o**, H_2-**3.1o**, and *dehydro*- **3.1k** were purchased from commercial suppliers and used as received. α-Hydroxy esters **3.1b-3.1i** were prepared in accordance with literature procedures.[58] α-Ketols **3.1j, 3.1l, 3.1m** and diol H_2-**3.1l** was prepared followed by the procedure by Rodrigues *et al.*[59] α-Ketol **3.1k** and *deuterio*-**3.1k** was prepared with the protocol by Sheldrick *et al.*[60] α-Ketol **3.1n** was synthesized by the method of Adam *et al.*[61] Diol **3.1j** was prepared from the corresponding alkene using the protocol described in the literature procedure reported by Hayashi *et al.*[62] Diol *dihydro*- **3.1k** was prepared in the accordance with the reported method described by Bar *et al.*[63] Diol H_2-**3.1m** and H_2- **3.1n** was prepared from the corresponding chromenes by OsO_4 catalyzed dihydroxylation.[64] Pressure tubes (13x100 mm, 15x100 mm or 15x125 mm) were flame dried followed by cooling in a desiccator. Toluene was dried over sodium metal, benzophenone, and distilled immediately prior to use. Anhydrous solvents were transferred by oven-dried syringes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40–63 μm). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Coupling constants are

reported in Hertz (Hz) for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δ_C (77.16 ppm).

Procedure for Synthesis of ethyl 2-hydroxy-2-(4-(methylthio)phenyl)acetate (3.1g).



To a flame-dried 50 mL round-bottom flask charged with ethyl 2-hydroxy-2-(4-(methylthio)phenyl)acetate (1.1 g, 4.9 mmol), was added ethanol (25 mL, 0.2 M). $NaBH_4$ (200 mg, 5.3 mmol) was added portionwise. The reaction mixture was allowed to stir at ambient temperature until the suspension became colorless. Distilled water was added and the reaction mixture was allowed to stir until bubbling stopped. The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (1 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was subjected to column chromatography (SiO_2: 20% ethyl acetate in hexanes) to give the title compound (0.93g, 4.1 mmol) in 84% yield as a white solid.

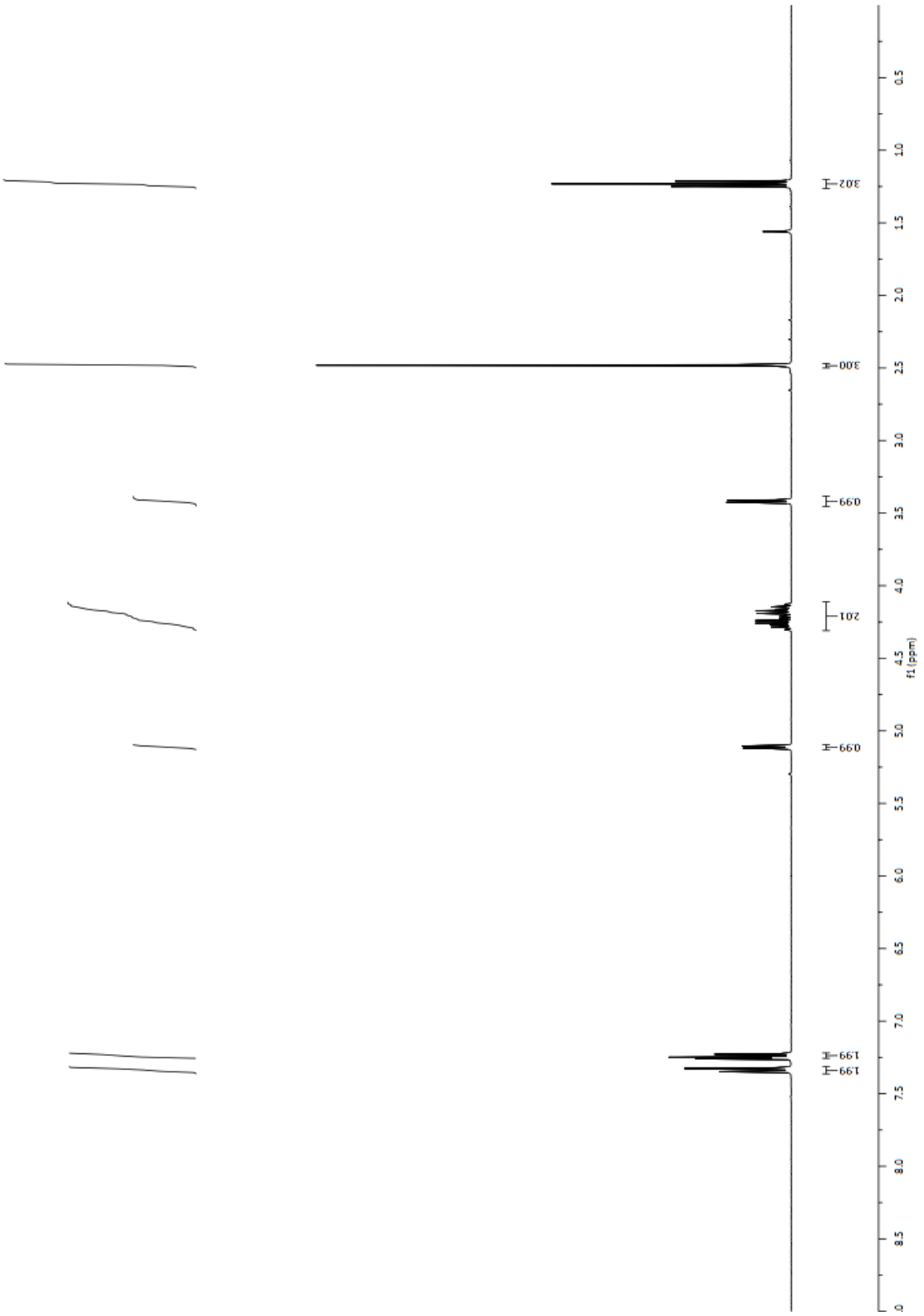
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.11 (d, *J* = 8.0 Hz 1H), 4.22 (m, 2H), 3.42 (d, *J* = 8.0 Hz, 1H), 2.48 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

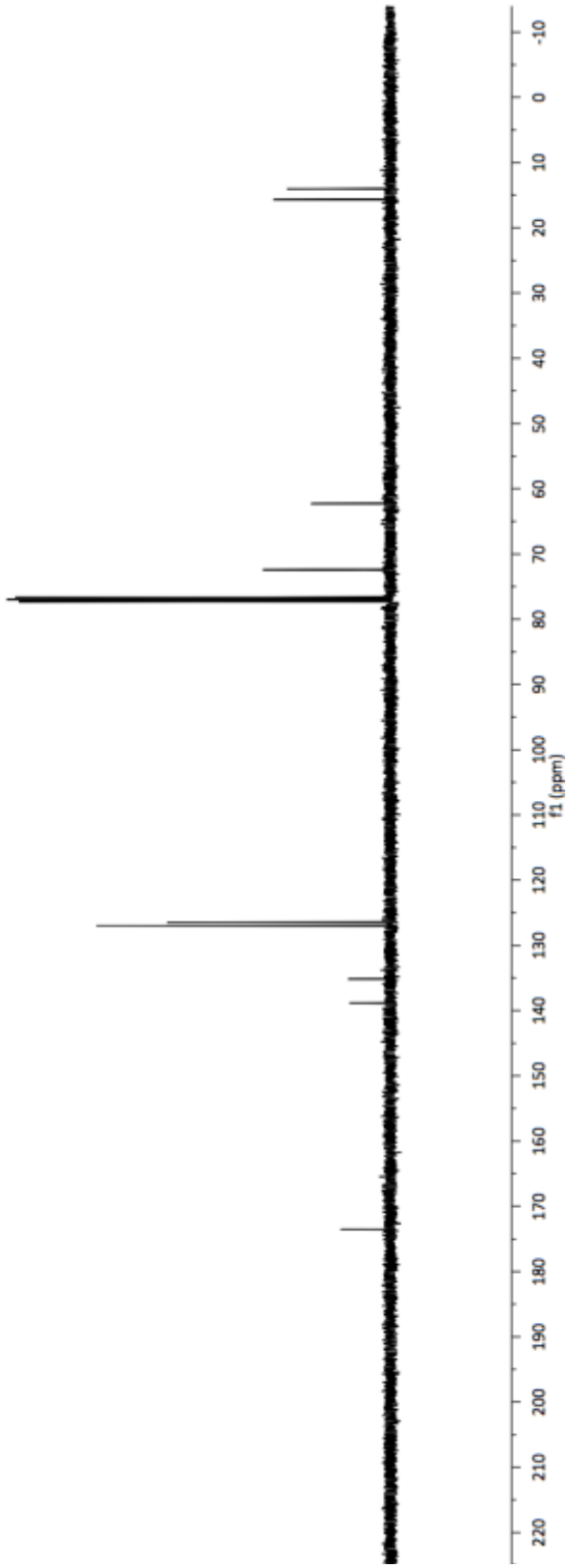
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 138.9, 135.2, 127.0, 126.5, 72.5, 62.3, 15.7, 14.0.

LRMS (ESI-MS) Calcd. for $C_{11}H_{14}O_3S$ $[M+Na]^+$: 249, Found: 249.

FTIR (neat): 3438, 2979, 1726.

MP: 91 °C.


3.02
3.00
0.99
2.01
0.99
1.99
1.99
f1 (ppm)


f1 (ppm)

General Procedure for Carbinol C-H Activation:

Procedure A

(For solid alcohol coupling partners): A resealable pressure tube (ca. 15 x 100 mm, 13 mL or 15 x 125 mm, 16 mL) was charged with $Os_3(CO)_{12}$ (5.5 mg, 0.006 mmol, 2 mol%) and XPhos (17.1 mg, 0.036 mmol, 12 mol%) and the reactant alcohol (0.30 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with ethylene. Toluene (0.15 mL, 2.0 M) was added and the rubber septum was quickly replaced with a screw cap. The reaction was allowed to stir at the stated temperature for the stated time. After cooling to room temperature, the mixture was evaporated under reduced pressure and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the indicated product.

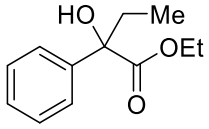
(For liquid alcohol coupling partners): A resealable pressure tube (ca. 15 x 100 mm, 13 mL or 15 x 125 mm, 16 mL) was charged with $Os_3(CO)_{12}$ (5.5 mg, 0.006 mmol, 2 mol%) and XPhos (17.1 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with ethylene. Toluene (0.15 mL, 2.0 M) and the reactant alcohol (0.30 mmol, 100 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The reaction was allowed to stir at the stated temperature for the stated time. After cooling to room temperature, the mixture was evaporated under reduced pressure and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the indicated product.

Procedure B

(For solid alcohol coupling partners): A resealable pressure tube (ca. 13 x 100 mm, 9 mL) was charged with $Os_3(CO)_{12}$ (3.7 mg, 0.004 mmol, 2 mol%), XPhos (11.4 mg, 0.024 mmol, 12 mol%), $AdCO_2H$ (3.6 mg, 0.02 mmol, 10 mol%) and the reactant alcohol (0.20 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with agron. 1-Octene (112.2 mg, 1.0 mmol, 500 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The reaction was allowed to stir at the stated temperature for the stated time. After cooling to room temperature, the mixture was evaporated under reduced pressure and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the indicated product.

(For liquid alcohol coupling partners): A resealable pressure tube (ca. 13 x 100 mm, 9 mL) was charged with $Os_3(CO)_{12}$ (3.7 mg, 0.004 mmol, 2 mol%), XPhos (11.4 mg, 0.024 mmol, 12 mol%) and $AdCO_2H$ (3.6 mg, 0.02 mmol, 10 mol%). The tube was sealed with a rubber septum and purged with argon. 1-Octene (112.2 mg, 1.0 mmol, 500 mol%) and the reactant alcohol (0.20 mmol, 100 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The reaction was allowed to stir at the stated temperature for the stated time. After cooling to room temperature, the mixture was evaporated under reduced pressure and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the indicated product.

Ethyl 2-hydroxy-2-phenylbutanoate (3.3a).



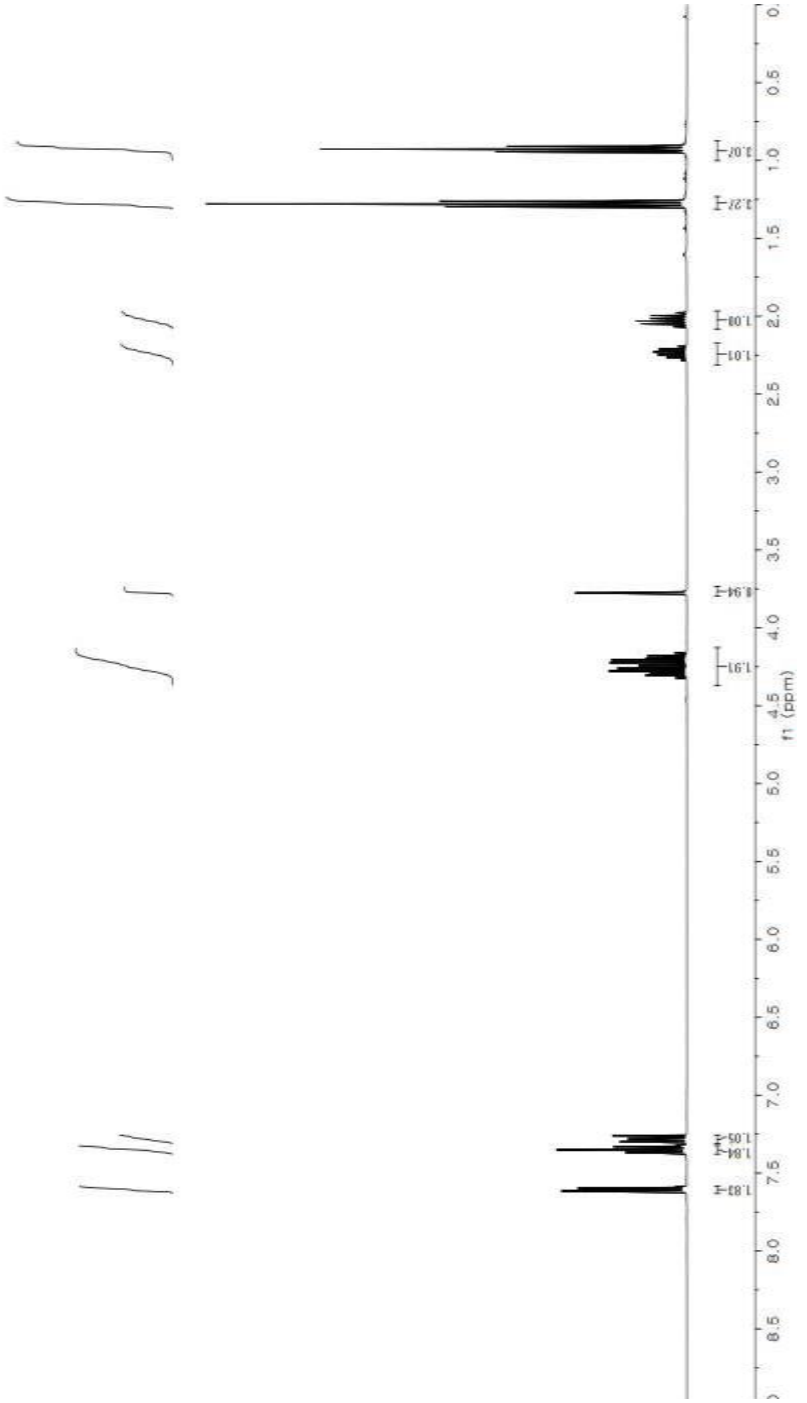
In accordance with Procedure A, **3.1a** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 2-5% ether/hexanes) provided the title compound (48.7 mg, 0.23 mmol) as a yellow oil in 78% yield.

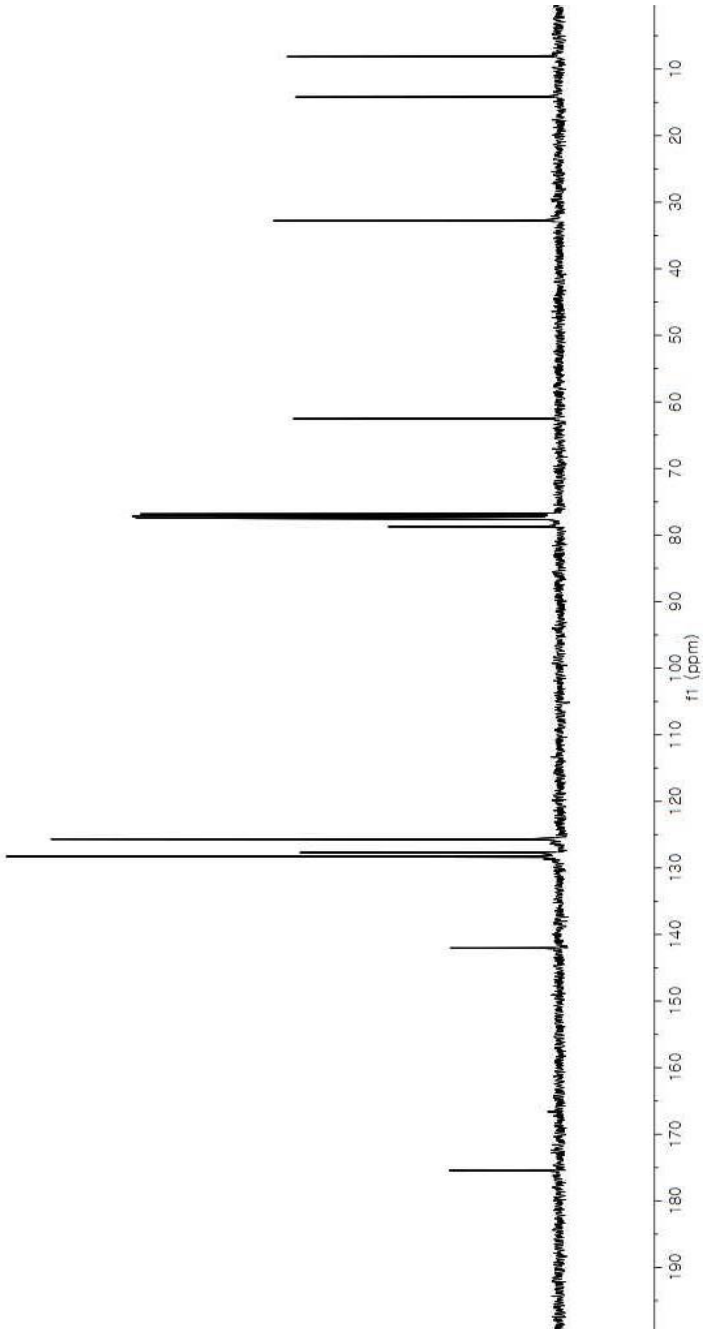
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62–7.59 (m, 2H), 7.37–7.32 (m, 2H), 7.30–7.26 (m, 1H), 4.32–4.16 (m, 2H), 3.78 (d, J = 0.4 Hz, 1H), 2.24 (dqd, J = 14.4, 7.2, 0.8 Hz, 1H), 2.07–1.98 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 142.0, 128.3, 127.7, 125.7, 78.7, 62.5, 32.8, 14.2, 8.2.

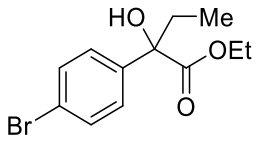
LRMS (ESI) Calcd. for $C_{12}H_{16}O_3$, $[M+Na]^+$: 231, Found: 231.

FTIR (neat): 3504, 2980, 1721.


1.00
1.27
1.08
1.01
1.94
1.91
1.05
1.84
1.83
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

Ethyl 2-(4-bromophenyl)-2-hydroxybutanoate (3.3b).



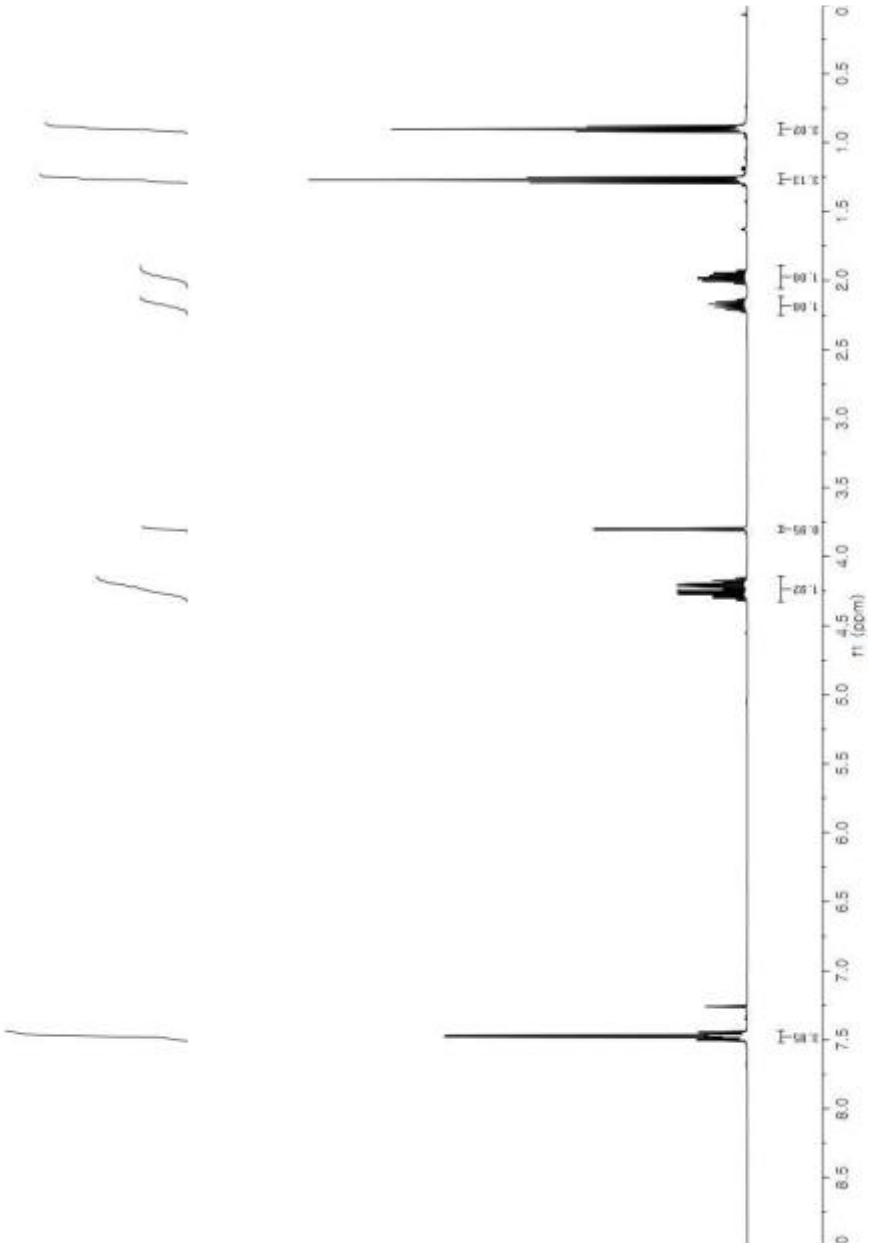
In accordance with Procedure A, **3.1b** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 2-4% ether/hexanes) provided the title compound (63.7 mg, 0.22 mmol) as a yellow oil in 74% yield.

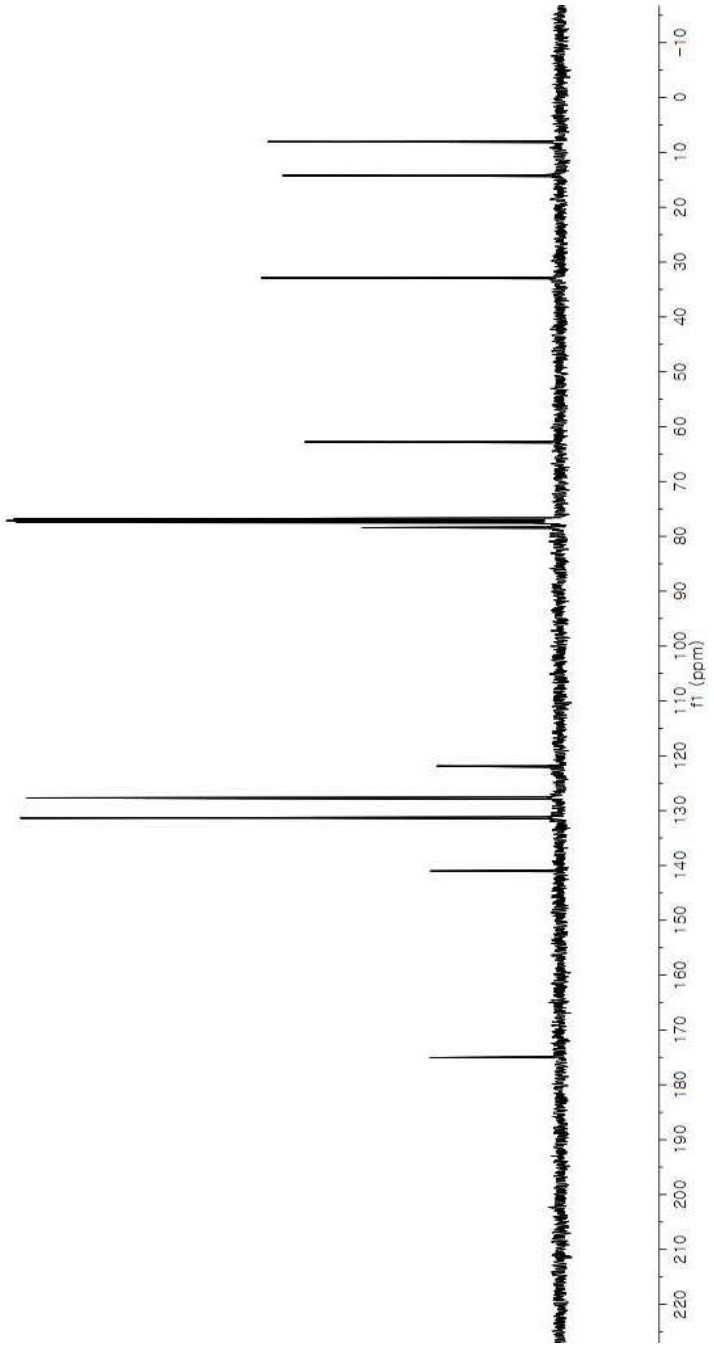
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.44 (m, 4H), 4.32–4.15 (m, 2H), 3.80 (d, *J* = 0.5 Hz, 1H), 2.24–2.12 (m, 1H), 1.97 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.99 (dd, *J* = 9.5, 5.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 141.0, 131.4, 127.7, 121.9, 78.4, 62.8, 32.9, 14.2, 8.1.

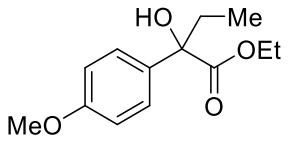
LRMS (ESI) Calcd. for $C_{12}H_{15}BrO_3$, $[M+Na]^+$: 309, 311, Found: 309, 311.

FTIR (neat): 3499, 2980, 1723.


f1 (ppm)


f1 (ppm)

Ethyl 2-hydroxy-2-(4-methoxyphenyl)butanoate (3.3c).



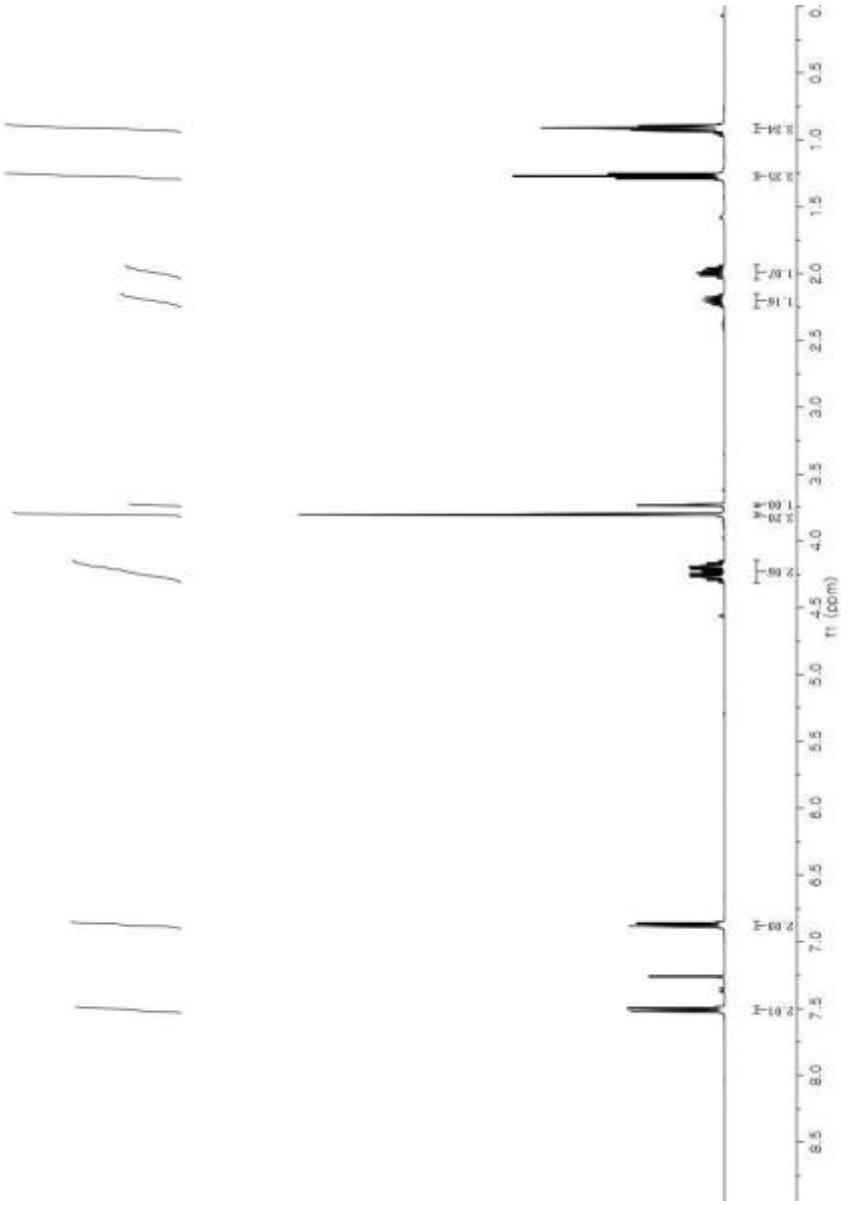
In accordance with Procedure A, **3.1c** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 50-100% dichloromethane/hexanes to 5% ethyl acetate/hexanes) provided the title compound (43.6 mg, 0.18 mmol) as a yellow oil in 61% yield.

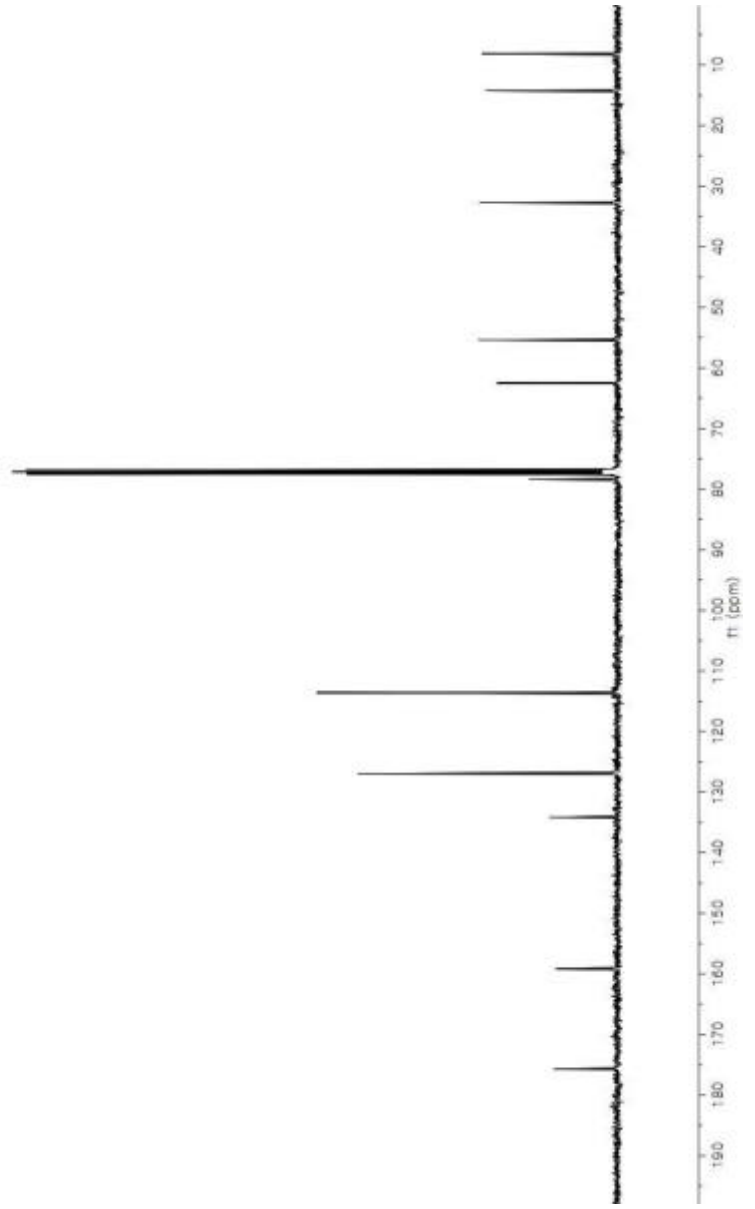
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.48 (m, 2H), 6.90–6.85 (m, 2H), 4.31–4.14 (m, 2H), 3.80 (s, 3H), 3.73 (s, 1H), 2.26–2.15 (m, 1H), 1.99 (dq, J = 14.6, 7.4 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 159.1, 134.2, 126.9, 113.6, 78.4, 62.5, 55.4, 32.8, 14.3, 8.2.

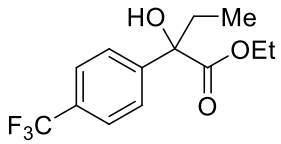
LRMS (ESI) Calcd. for $C_{13}H_{18}O_4$, $[M+Na]^+$: 261, Found: 261.

FTIR (neat): 3511, 2970, 1721.


f1 (ppm)


f1 (ppm)

Ethyl 2-hydroxy-2-(4-(trifluoromethyl)phenyl)butanoate (3.3d).



In accordance with Procedure A, **3.1d** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 1-5% ether/hexanes) provided the title compound (63.8 mg, 0.23 mmol) as a yellow oil in 77% yield.

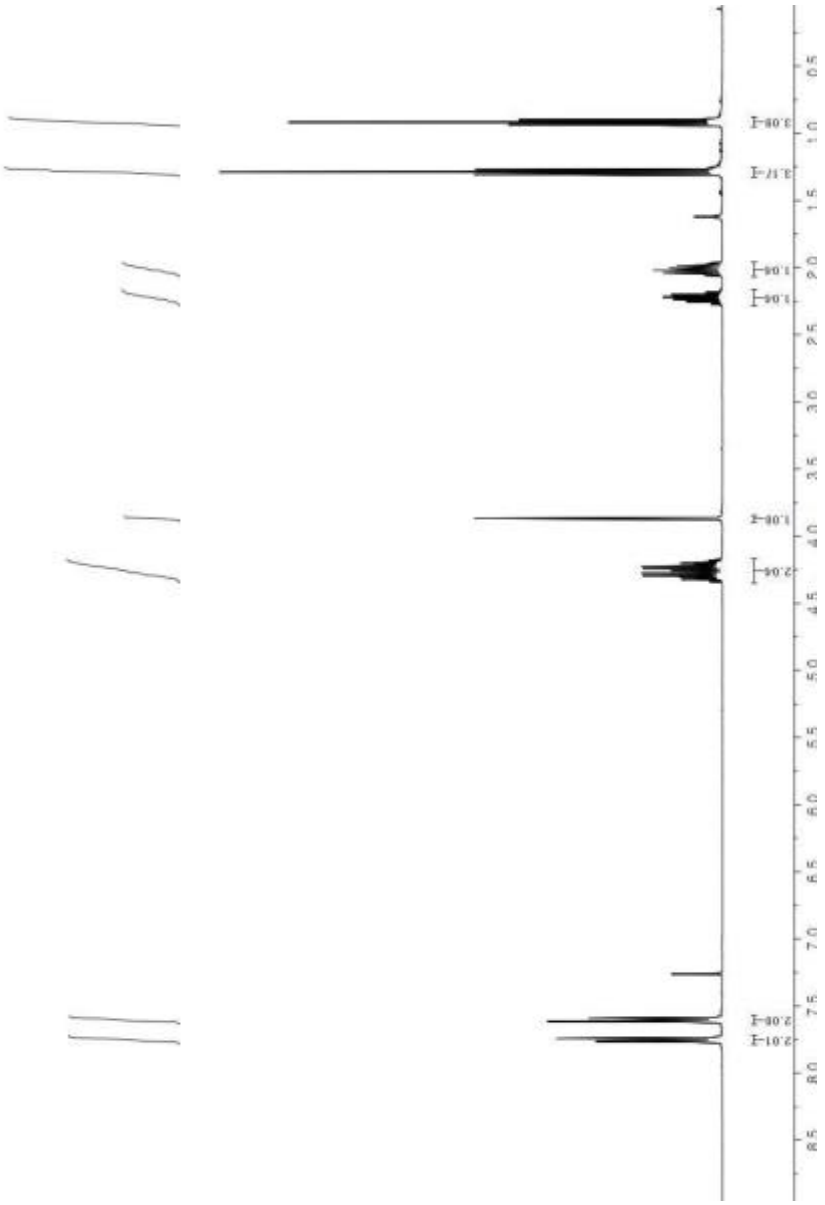
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.72 (m, 2H), 7.64–7.57 (m, 2H), 4.35–4.17 (m, 2H), 3.87 (s, 1H), 2.23 (dq, J = 14.5, 7.2 Hz, 1H), 2.01 (dq, J = 14.5, 7.4 Hz, 1H), 1.28 (t, J = 6.2 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H).

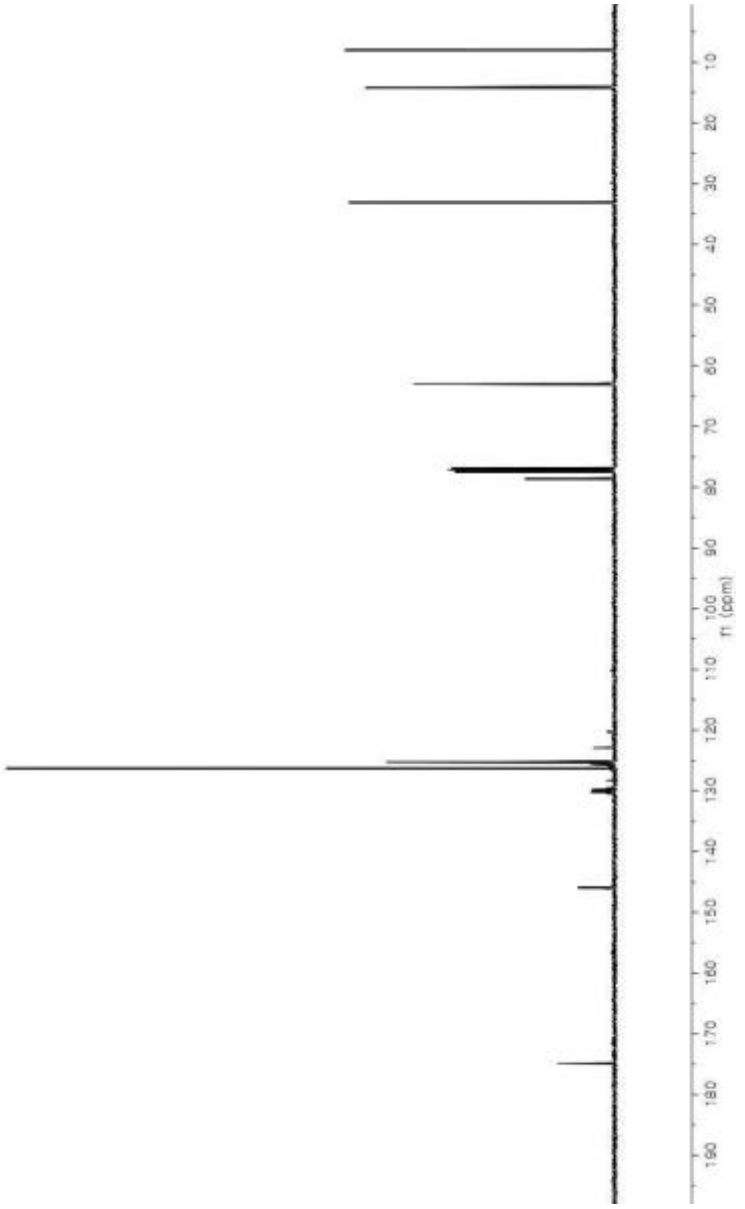
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 145.9, 130.0 (q, J = 32.0 Hz), 126.3, 125.2 (q, J = 4.0 Hz), 124.3 (q, J = 271.0 Hz), 78.6, 63.0, 33.1, 14.2, 8.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.6.

LRMS (ESI) Calcd. for $C_{13}H_{15}F_3O_3$, $[M+Na]^+$: 299, Found: 299.

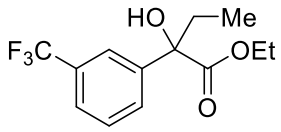
FTIR (neat): 3510, 2985, 1726.




f1 (ppm)

f1 (ppm)

Ethyl 2-hydroxy-2-(3-(trifluoromethyl)phenyl)butanoate (3.3e).



In accordance with Procedure A, **3.1e** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 2-5% ether/hexanes) provided the title compound (63.0 mg, 0.23 mmol) as a yellow oil in 76% yield.

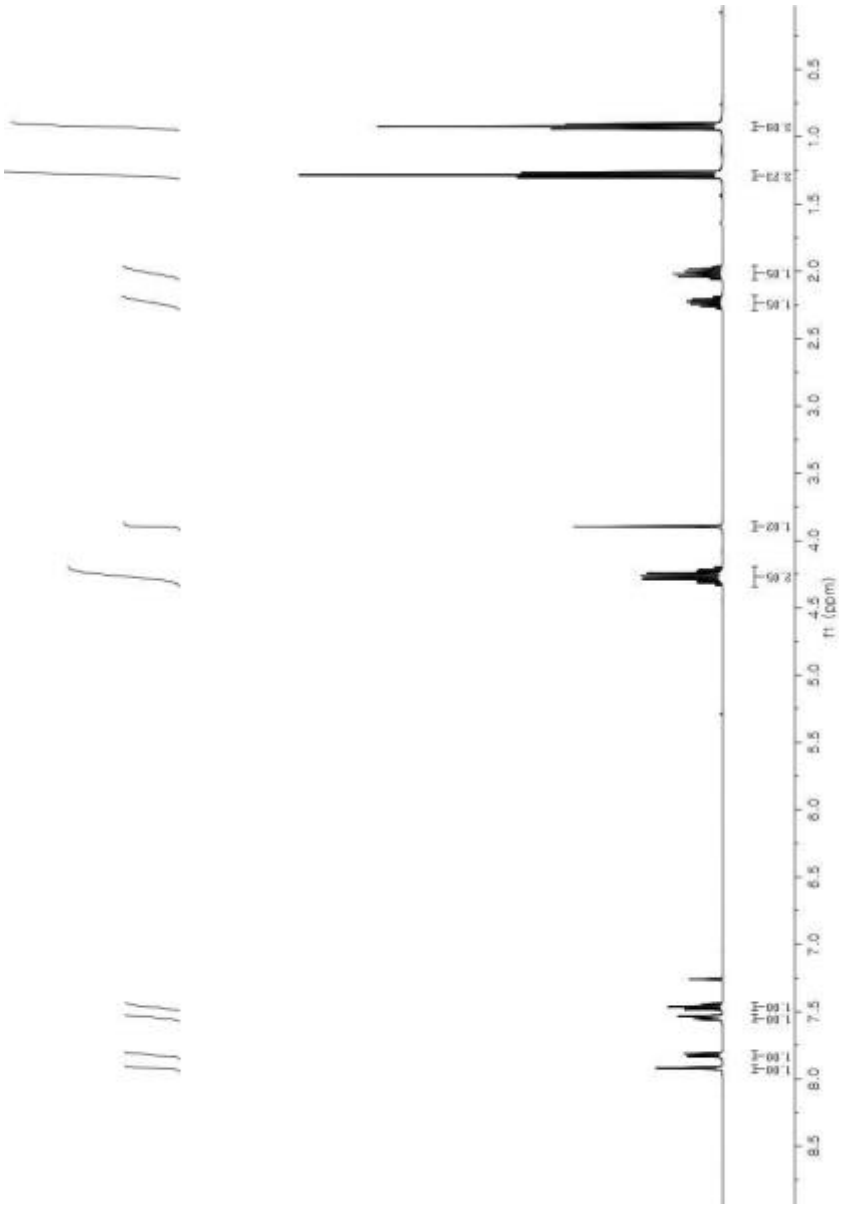
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.86–7.79 (m, 1H), 7.55 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.46 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.34–4.19 (m, 2H), 3.90 (d, *J* = 0.5 Hz, 1H), 2.29–2.18 (m, 1H), 2.01 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

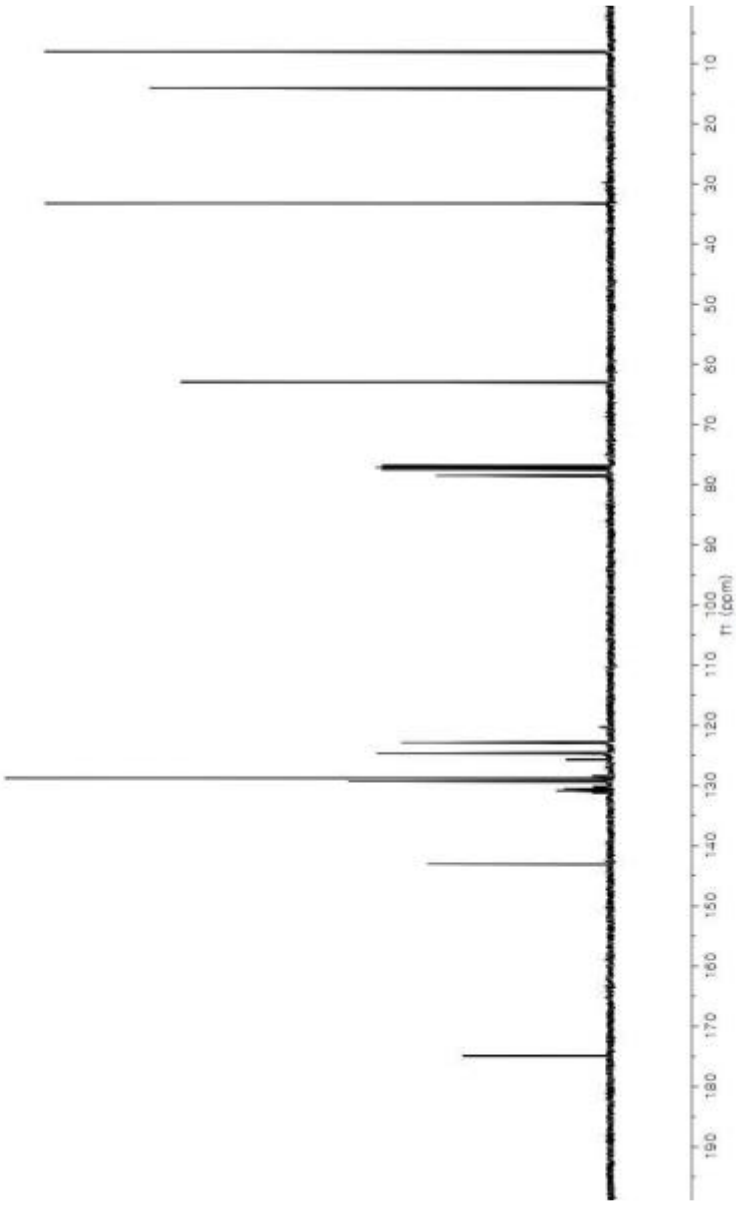
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 143.1, 130.7 (q, *J* = 32.0 Hz), 129.3, 128.8, 124.6 (q, *J* = 3.7 Hz), 124.3 (q, *J* = 271.0 Hz), 122.9 (q, *J* = 4.0 Hz), 78.5, 63.0, 33.2, 14.2, 8.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -62.6.

LRMS (ESI) Calcd. for $C_{13}H_{15}F_3O_3$, $[M+Na]^+$: 299, Found: 299.

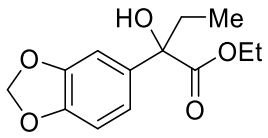
FTIR (neat): 3513, 2985, 1725.


f1 (ppm)


f1 (ppm)

f1 (ppm)

Ethyl 2-(benzo[d][1,3]dioxol-5-yl)-2-hydroxybutanoate (3.3f).



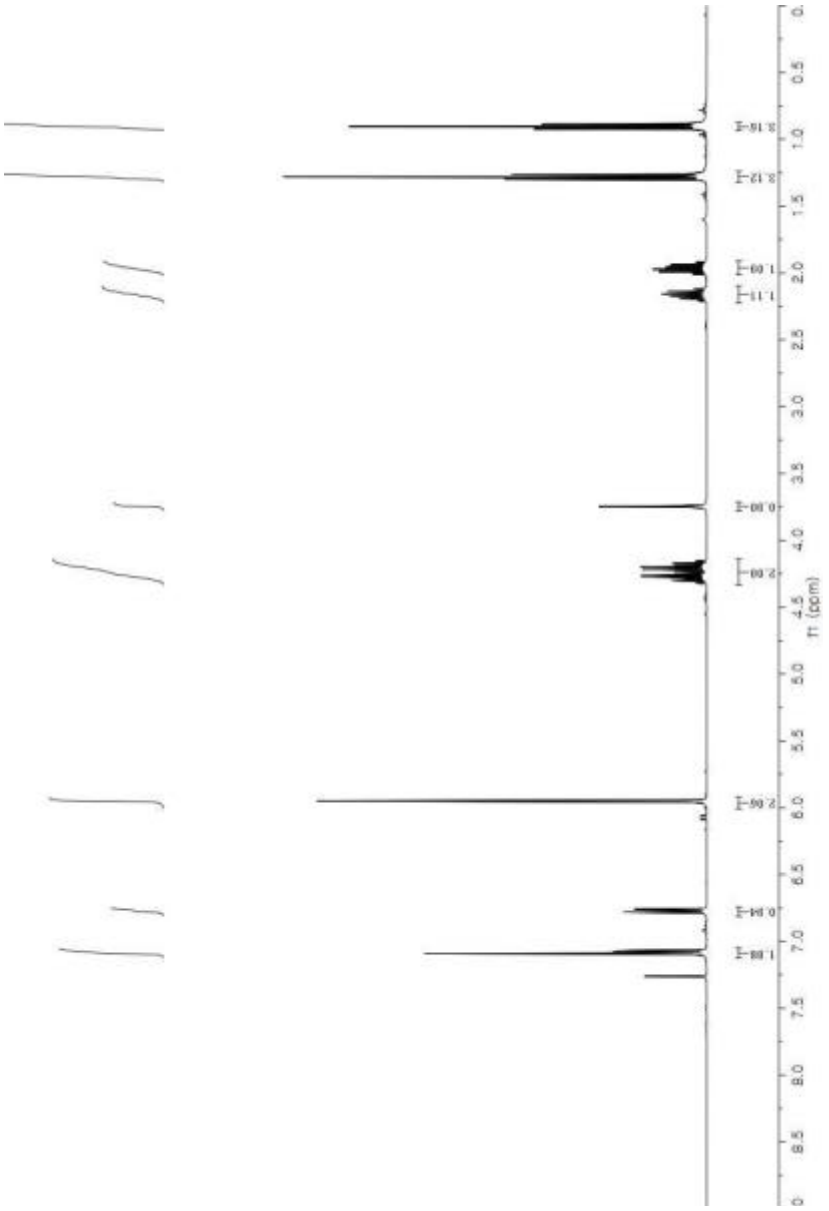
In accordance with Procedure A, **3.1f** (0.2 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 290 mol%) in toluene (2.0 M) at 140 °C for a 40 hour period. Flash column chromatography (SiO_2: 3-5% ether/hexanes) provided the title compound (30.8 mg, 0.12 mmol) as a colorless oil in 61% yield. NOTE: $Os_3(CO)_{12}$ (3.6 mg, 0.004 mmol, 2 mol%) and XPhos (11.4 mg, 0.024 mmol, 12 mol%)

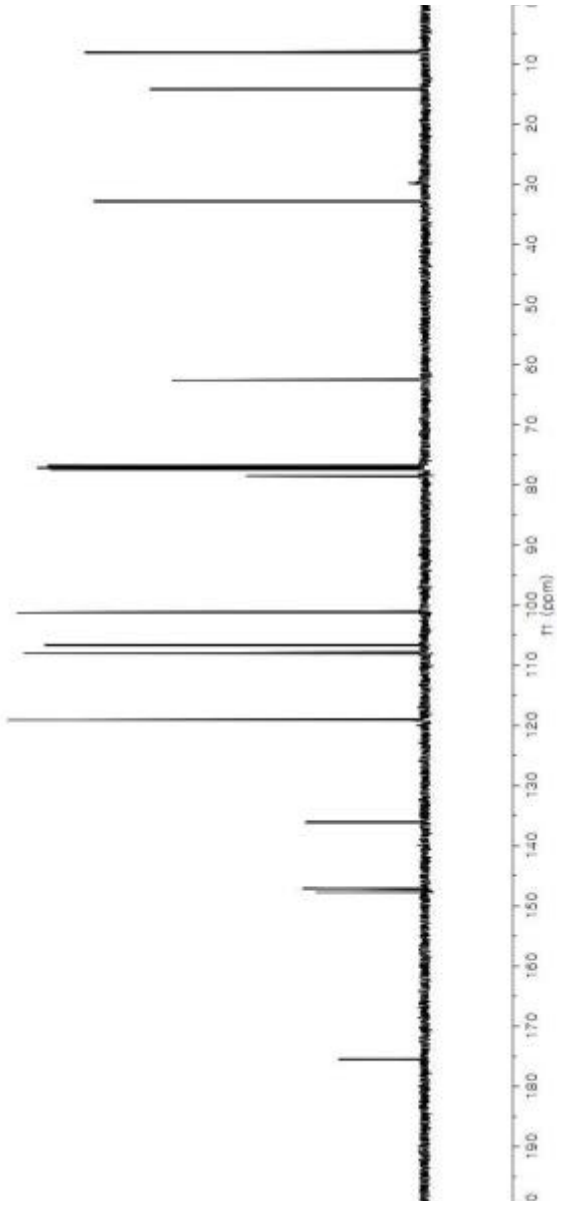
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–7.05 (m, 2H), 6.77 (dd, J = 7.5, 1.1 Hz, 1H), 6.01–5.92 (m, 2H), 4.33–4.14 (m, 2H), 3.75 (s, 1H), 2.16 (dq, J = 14.4, 7.2 Hz, 1H), 1.96 (dq, J = 14.7, 7.4 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 147.7, 147.1, 136.1, 119.1, 107.9, 106.7, 101.2, 78.5, 62.6, 32.9, 14.3, 8.1.

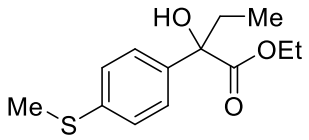
LRMS (ESI) Calcd. for $C_{13}H_{16}O_5$, $[M+Na]^+$: 275, Found: 275.

FTIR (neat): 3507, 2971, 1722.


f1 (ppm)


f1 (ppm)

Ethyl 2-hydroxy-2-(4-(methylthio)phenyl)butanoate (3.3g).



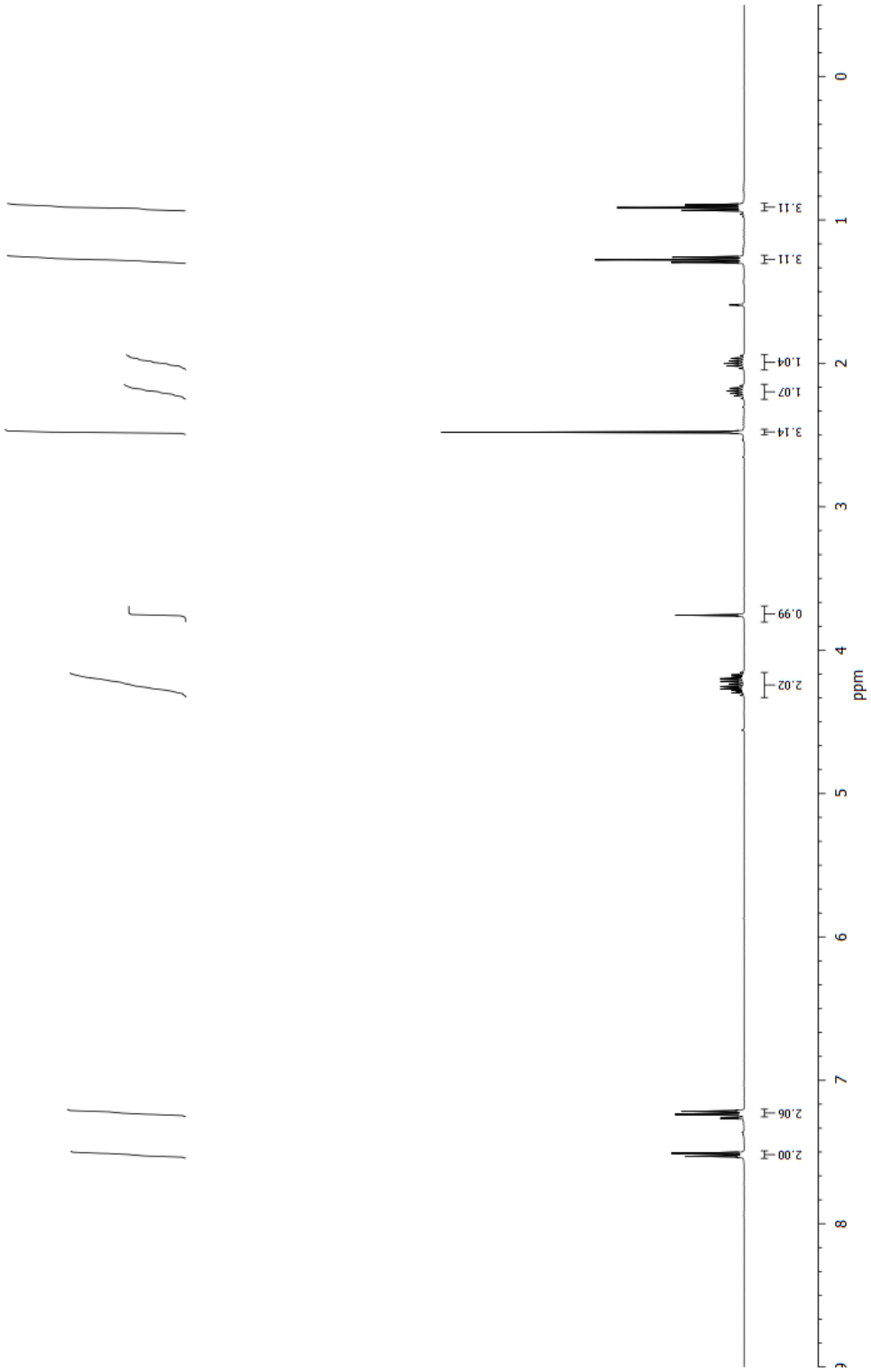
In accordance with Procedure A, **3.1g** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 2-5% ether/hexanes) provided the title compound (30.8 mg, 0.18 mmol) as a yellow oil in 61% yield.

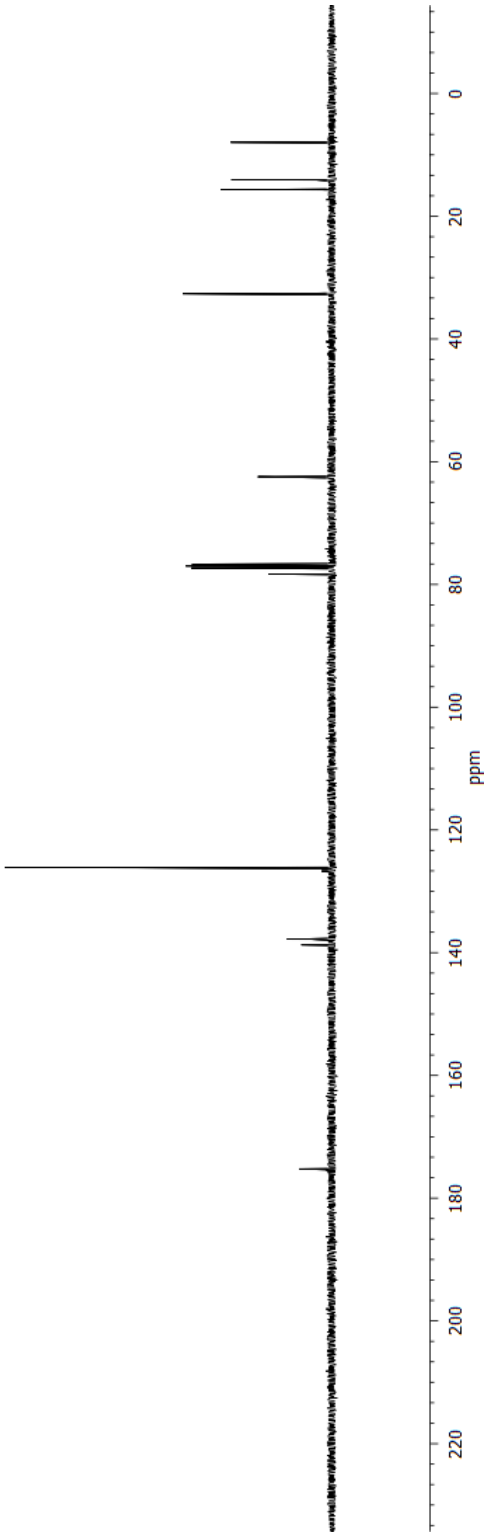
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.48 (m, 2H), 7.26–7.20 (m, 2H), 4.37–4.10 (m, 2H), 3.76 (s, 1H), 2.48 (s, 3H), 2.25–2.15 (m, 1H), 2.04-1.95 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 138.7, 137.8, 126.2, 126.1 78.3, 62.4, 32.6, 15.7, 14.1, 7.9.

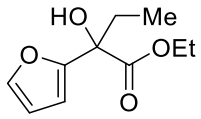
LRMS (ESI) Calcd. for $C_{13}H_{18}O_3S$, $[M+Na]^+$: , Found: 277

FTIR (neat): 3507, 2979, 1721.


3.11
3.11
1.04
1.07
3.14
0.99
2.02
2.06
2.00
ppm


0
20
40
60
80
100
120
140
160
180
200
220
ppm

Ethyl 2-(furan-2-yl)-2-hydroxybutanoate (3.3h).



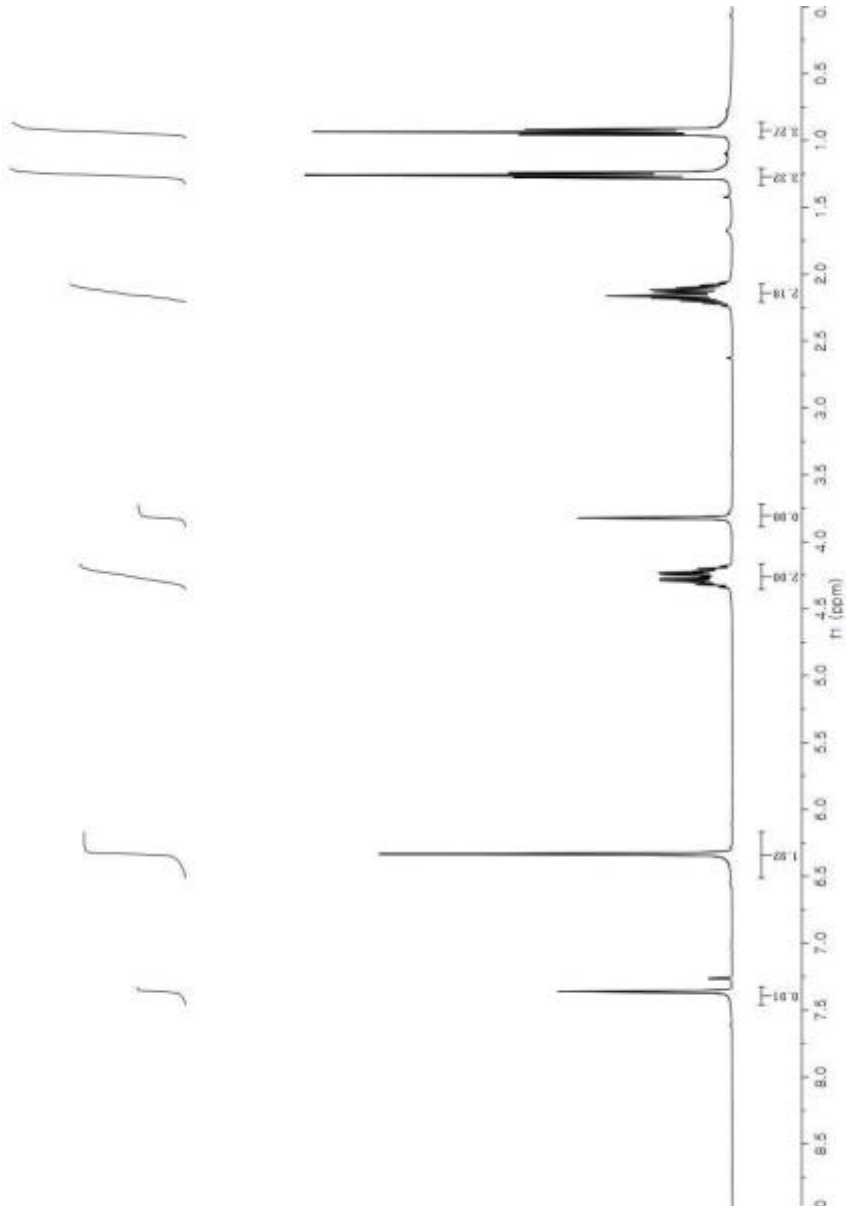
In accordance with Procedure A, **3.1h** (0.2 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 290 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 3-5% ether/hexanes) provided the title compound (25.0 mg, 0.13 mmol) as a yellow oil in 64% yield.

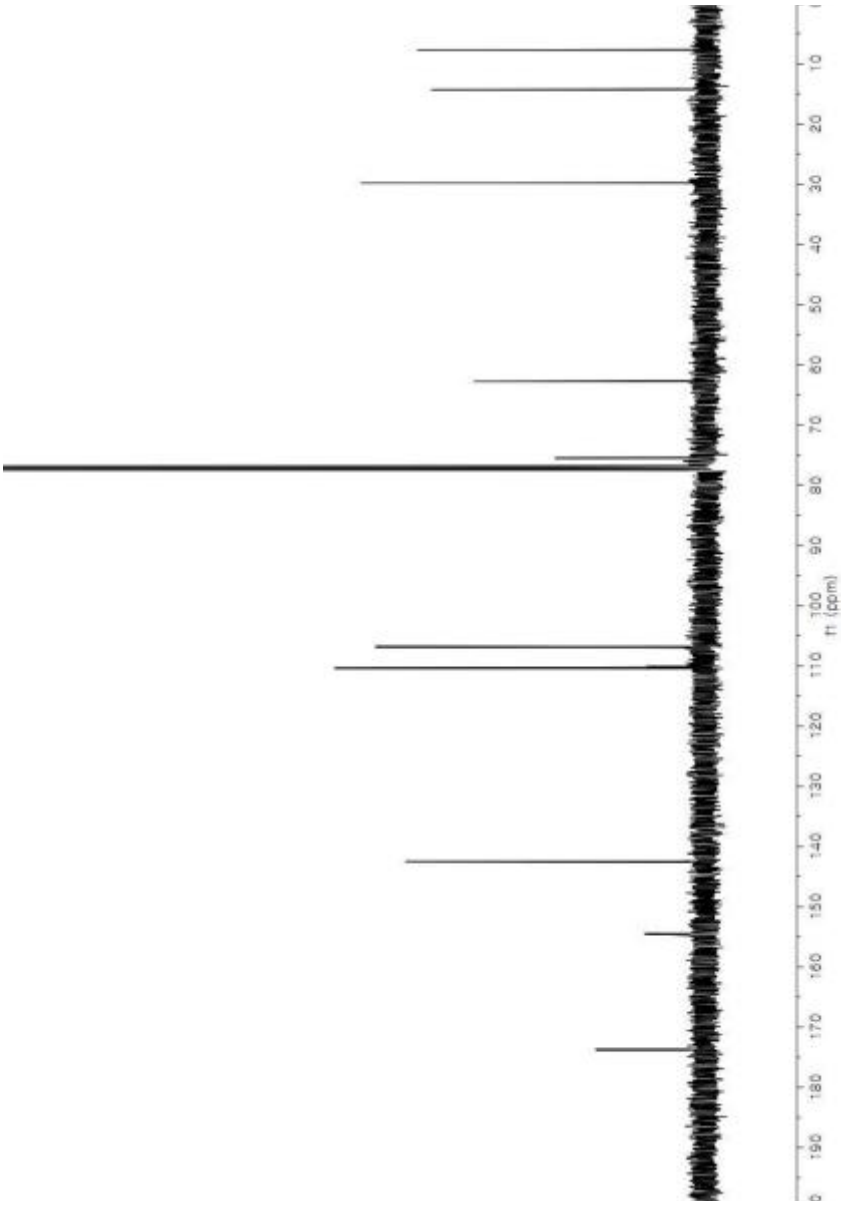
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 1.1 Hz, 1H), 6.33 (s, 2H), 4.36–4.14 (m, 2H), 3.82 (s, 1H), 2.21–2.07 (m, 2H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 154.5, 142.5, 110.4, 106.8, 75.5, 62.8, 29.8, 14.3, 7.7.

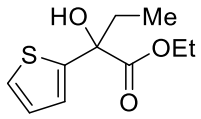
LRMS (ESI) Calcd. for $C_{10}H_{14}O_4$, $[M+Na]^+$: 221, Found: 221

FTIR (neat): 3511, 2970, 1728.


f1 (ppm)


f1 (ppm)

Ethyl 2-hydroxy-2-(thiophen-2-yl)butanoate (3.3i).



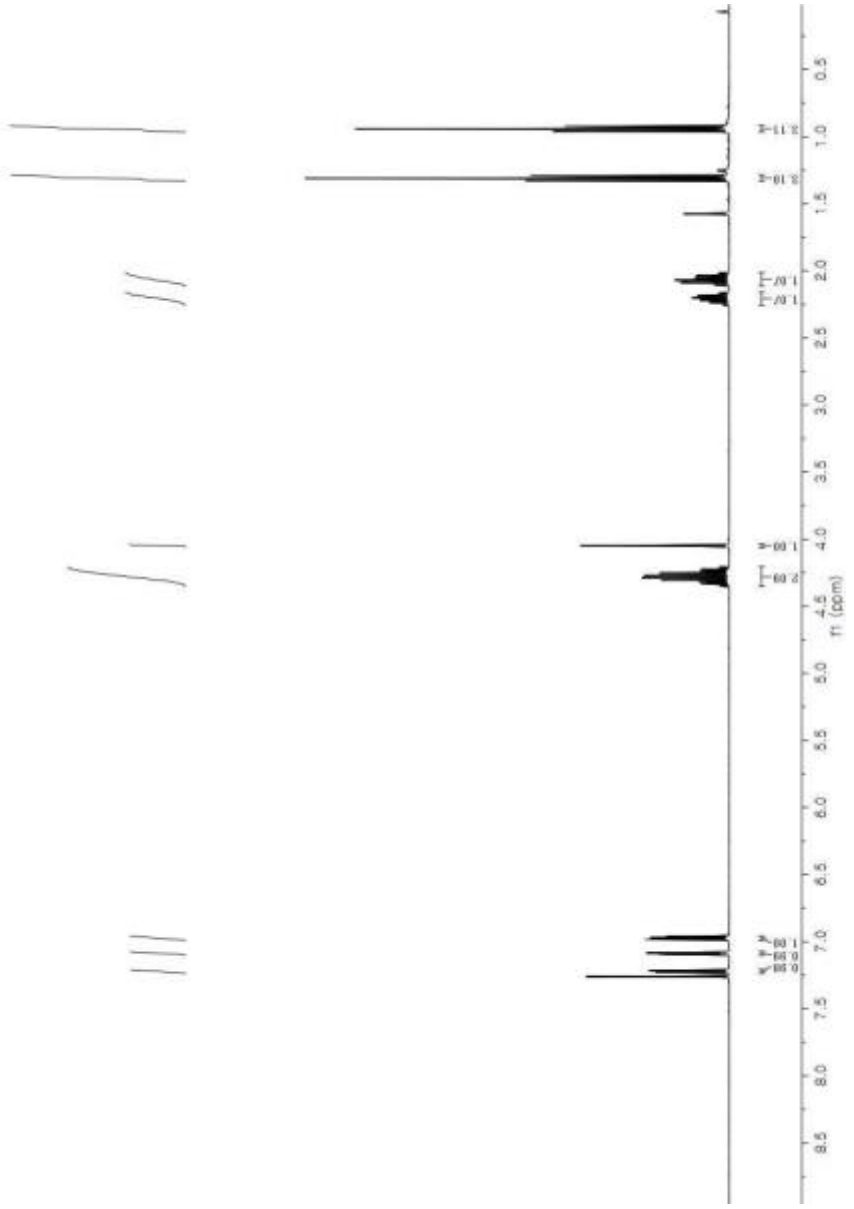
In accordance with Procedure A, **3.1i** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 30-50% dichloromethane/hexanes) provided the title compound (45.0 mg, 0.22 mmol) as a colorless oil in 70% yield.

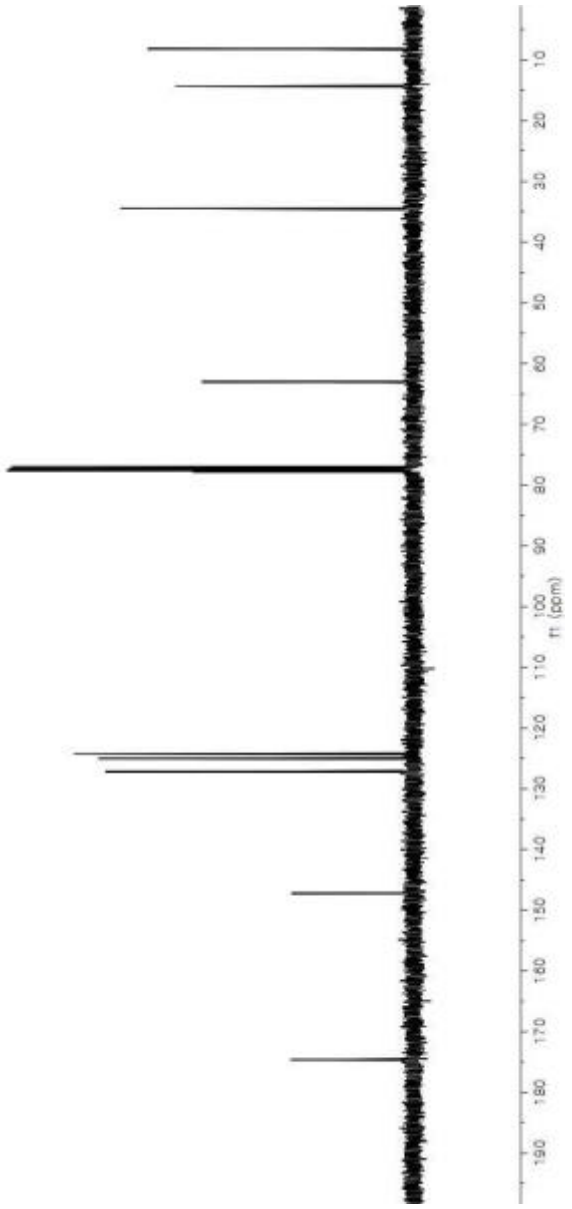
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.09 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.35–4.21 (m, 2H), 4.05 (d, *J* = 0.8 Hz, 1H), 2.26–2.16 (m, 1H), 2.06 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 147.1, 127.1, 124.9, 124.1, 77.7, 62.9, 34.4, 14.2, 8.1.

LRMS (ESI) Calcd. for $C_{10}H_{14}O_3S$, $[M+Na]^+$: 237, Found: 237.

FTIR (neat): 3499, 2979, 1724.


f1 (ppm)


10
20
30
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60
70
80
90
100
110
120
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140
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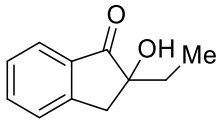
170
180
190
f1 (ppm)

2-Ethyl-2-hydroxy-2,3-dihydro-1H-inden-1-one (3.3j).



Using ketol

In accordance with Procedure A, **3.1j** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 140 °C for a 40 hour period. Flash column chromatography (SiO_2: 5-15% ethyl acetate/hexanes) provided the title compound (44.4 mg, 0.25 mmol) as a yellow oil in 84% yield.

Using diol

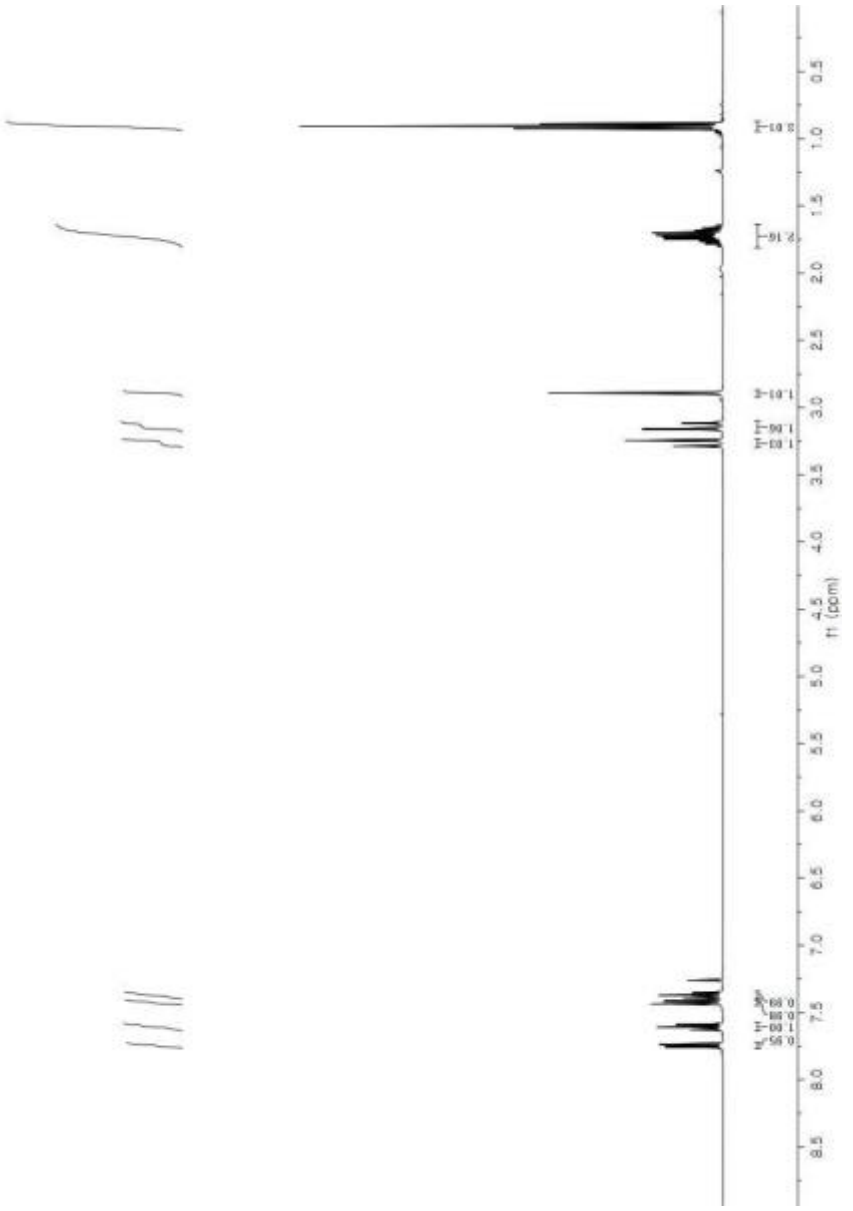
In accordance with Procedure A, H_2-**3.1j** (0.15 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 390 mol%) in toluene (1.5 M) at 140 °C for a 48 hour period. Flash column chromatography (SiO_2: 5-15% ethyl acetate/hexanes) provided the title compound (18.8 mg, 0.11 mmol) as a yellow oil in 71% yield. NOTE: $Os_3(CO)_{12}$ (2.7 mg, 0.003 mmol, 2 mol%), XPhos (8.5 mg, 0.018 mmol, 12 mol%).

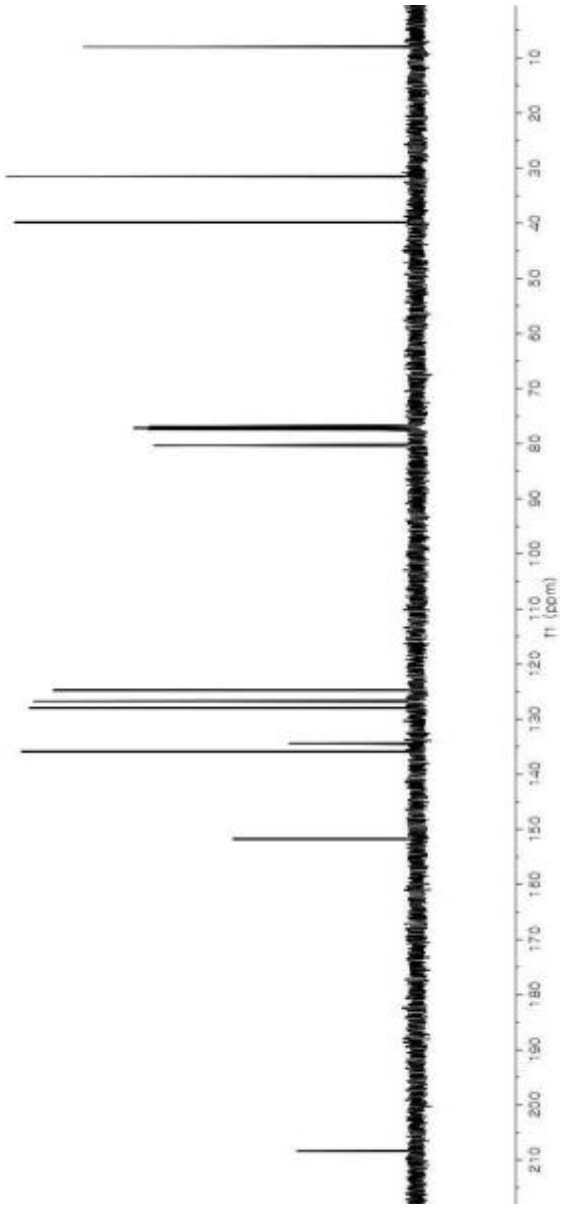
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.72 (m, 1H), 7.61 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.45–7.41 (m, 1H), 7.40–7.34 (m, 1H), 3.27 (d, J = 17.0 Hz, 1H), 3.14 (d, J = 17.0 Hz, 1H), 2.89 (s, 1H), 1.81–1.64 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4, 151.7, 135.9, 134.4, 127.9, 126.7, 124.7, 80.3, 39.8, 31.6, 8.0.

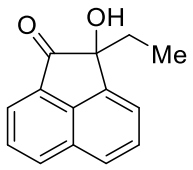
LRMS (ESI) Calcd. for $C_{11}H_{12}O_2$, $[M+Na]^+$: 199, Found: 199.

FTIR (neat): 3413, 2967, 1709.


f1 (ppm)


f1 (ppm)

2-Ethyl-2-hydroxyacenaphthylen-1(2H)-one (3.3k).



Using ketol

In accordance with Procedure A, **3.3k** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 48 hour period. Flash column chromatography (SiO_2: 5-15% ethyl acetate/hexanes) provided the title compound (40.1 mg, 0.18 mmol) as a yellow solid in 63% yield.

Using diol

In accordance with Procedure A, H_2-**3.1k** (0.15 mmol, 100 mol%) was reacted with ethylene (15 x 125 mm pressure tube, 0.71 mmol, 480 mol%) in toluene (1.5 M) at 140 °C for a 48 hour period. Flash column chromatography (SiO_2: 5-15% ethyl acetate/hexanes) provided the title compound (21.3 mg, 0.11 mmol) as a yellow solid in 70% yield. NOTE: $Os_3(CO)_{12}$ (2.7 mg, 0.003 mmol, 2 mol%), XPhos (8.5 mg, 0.018 mmol, 12 mol%) and $AdCO_2H$ (2.7 mg, 0.015mmol, 10 mol%).

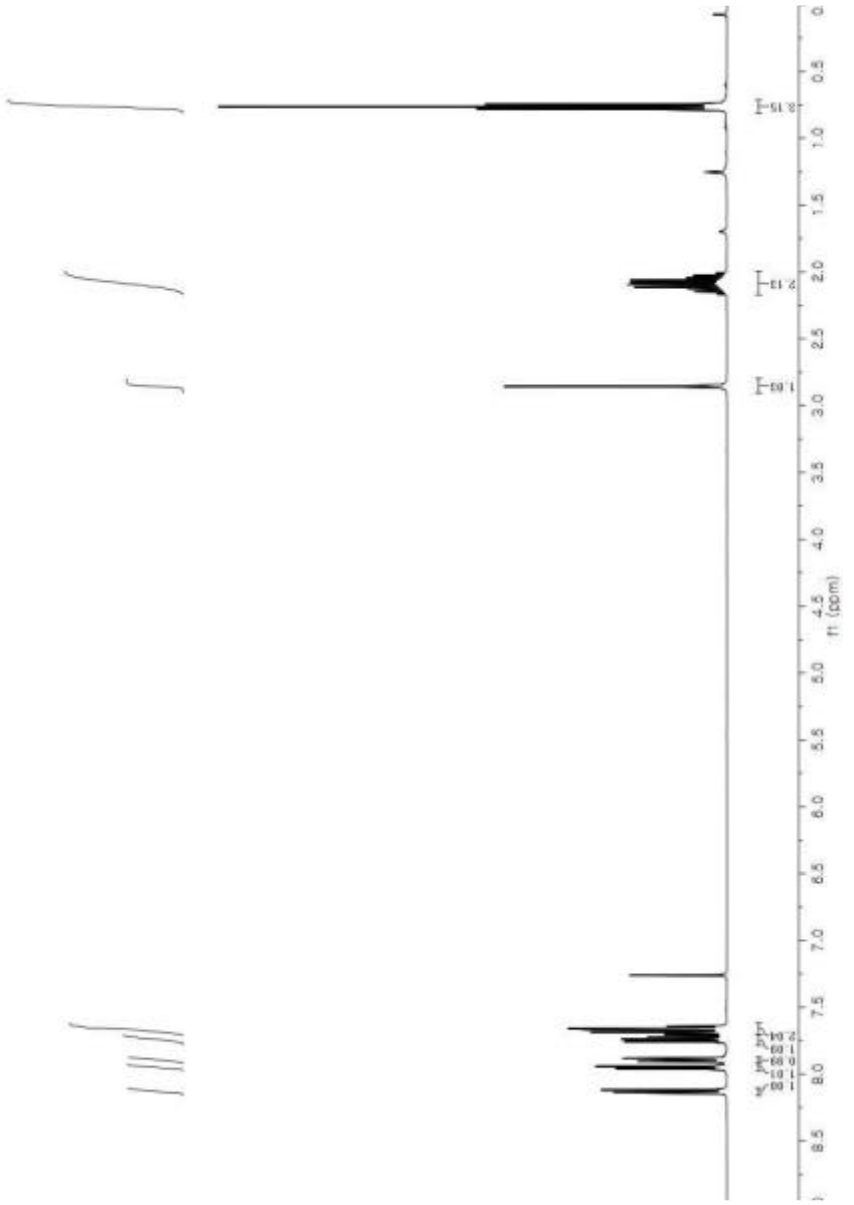
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 7.0 Hz, 1H), 7.89 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.74 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.71–7.62 (m, 2H), 2.86 (s, 1H), 2.17–1.99 (m, 2H), 0.76 (t, *J* = 7.5 Hz, 3H).

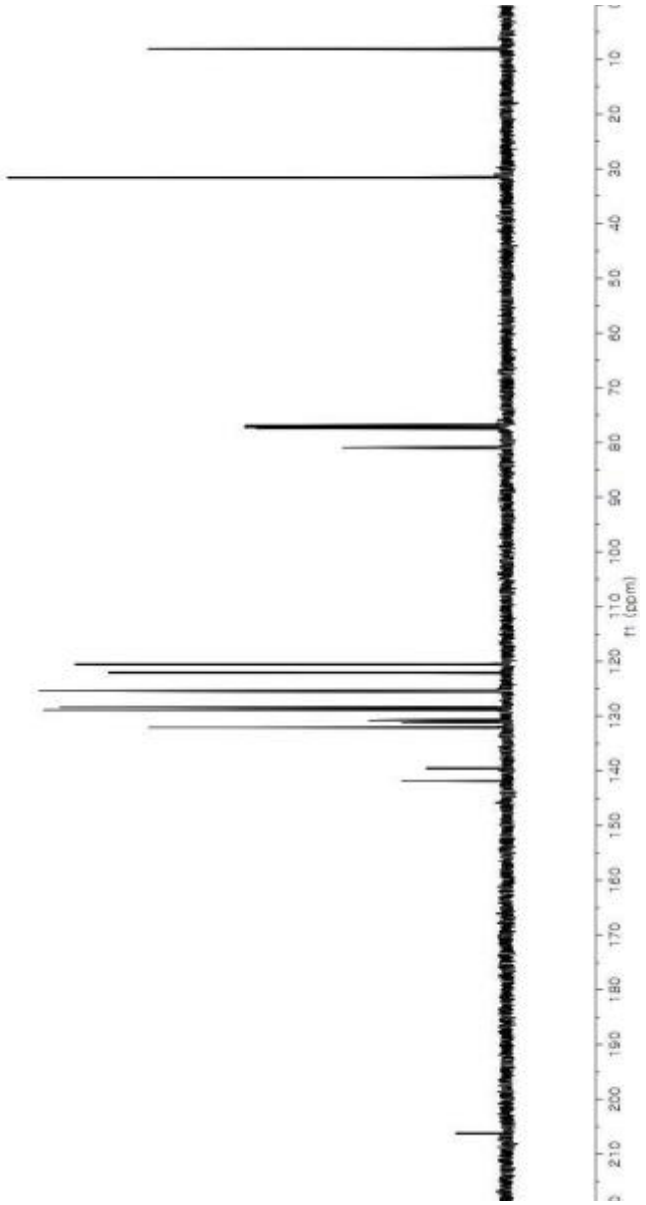
^{13}C NMR (100 MHz, $CDCl_3$): δ 206.2, 141.8, 139.5, 132.1, 131.2, 130.8, 128.9, 128.4, 125.4, 122.0, 120.5, 80.9, 31.6, 8.2.

LRMS (ESI) Calcd. for $C_{14}H_{12}O_2$, $[M+Na]^+$: 235, Found: 235.

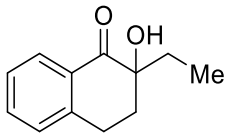
FTIR (neat): 3369, 2970, 2931, 1716.

MP: 92.7–93.1 °C.


f1 (ppm)


f1 (ppm)

2-Ethyl-2-hydroxy-3,4-dihydronaphthalen-1(2H)-one (3.3l).



Using ketol

In accordance with Procedure A, **3.1l** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 140 °C for a 40 hour period. Flash column chromatography (SiO_2: 5-7% ethyl acetate/hexanes) provided the title compound (47.4 mg, 0.25 mmol) as a brown oil in 83% yield. NOTE: $AdCO_2H$ (5.4 mg, 0.03mmol, 10 mol%)

Using diol

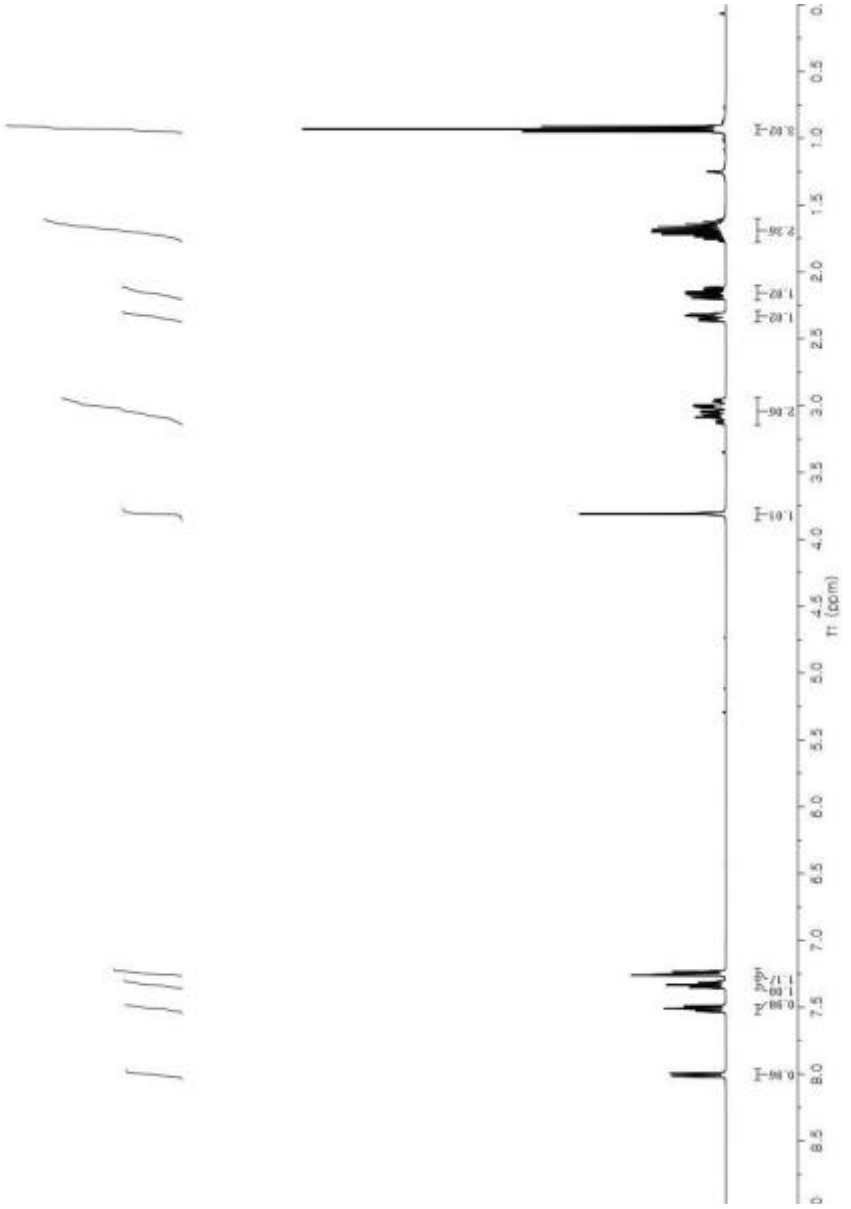
In accordance with Procedure A, H_2-**3.1l** (0.15 mmol, 100 mol%) was reacted with ethylene (15 x 125 mm pressure tube, 0.71 mmol, 480 mol%) in toluene (1.5 M) at 140 °C for a 48 hour period. Flash column chromatography (SiO_2: 5-7% ethyl acetate/hexanes) provided the title compound (20.3 mg, 0.11 mmol) as a brown oil in 71% yield. NOTE: $Os_3(CO)_{12}$ (2.7 mg, 0.003 mmol, 2 mol%), XPhos (8.5 mg, 0.018 mmol, 12 mol%) and $AdCO_2H$ (2.7 mg, 0.015mmol, 10 mol%).

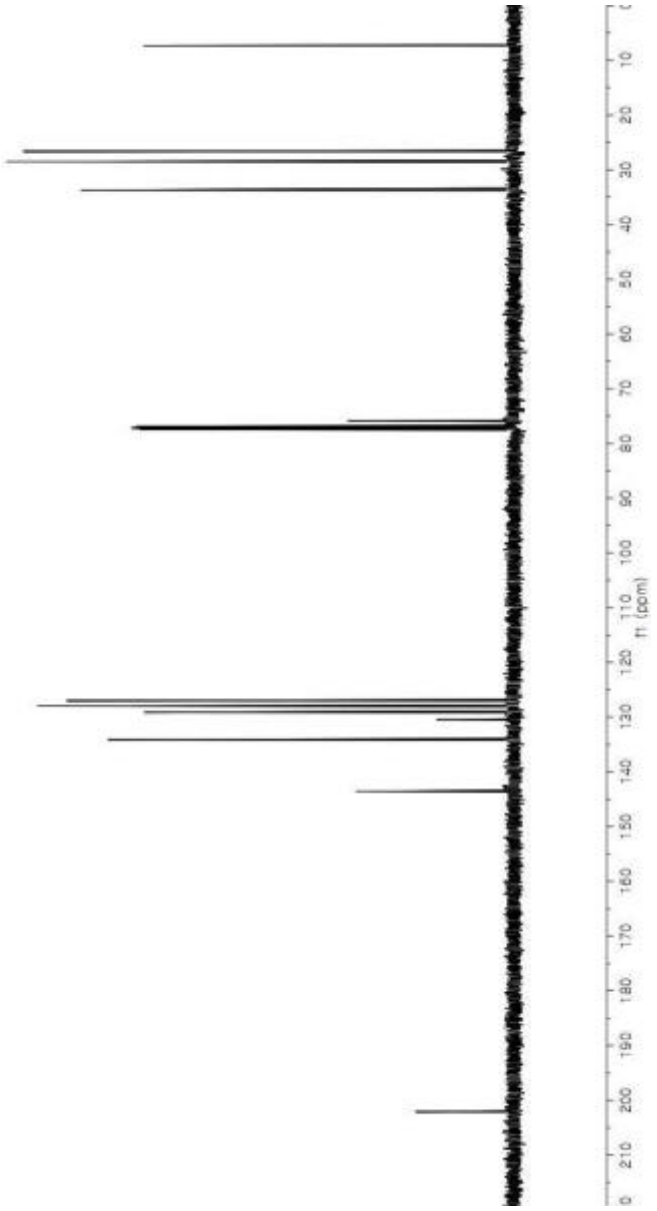
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.51 (ddd, *J* = 7.5, 7.5, 1.4 Hz, 1H), 7.33 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.27–7.21 (m, 1H), 3.81 (s, 1H), 3.15–2.94 (m, 2H), 2.34 (ddd, *J* = 13.5, 5.1, 2.3 Hz, 1H), 2.21–2.10 (m, 1H), 1.78–1.60 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 143.6, 134.1, 130.4, 129.1, 128.0, 127.0, 75.9, 33.7, 28.5, 26.6, 7.3.

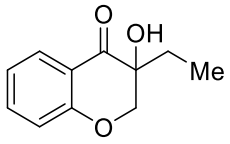
LRMS (ESI) Calcd. for $C_{12}H_{14}O_2$, $[M+Na]^+$: 213, Found: 213.

FTIR (neat): 3488, 2931, 1681.


f1 (ppm)


f1 (ppm)

3-Ethyl-3-hydroxychroman-4-one (3.3m).



Using ketol

In accordance with Procedure A, **3.1m** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 48 hour period. Flash column chromatography (SiO_2: 2-4% ethyl acetate/hexanes) provided the title compound (49.6 mg, 0.26 mmol) as a yellow oil in 86% yield.

Using diol

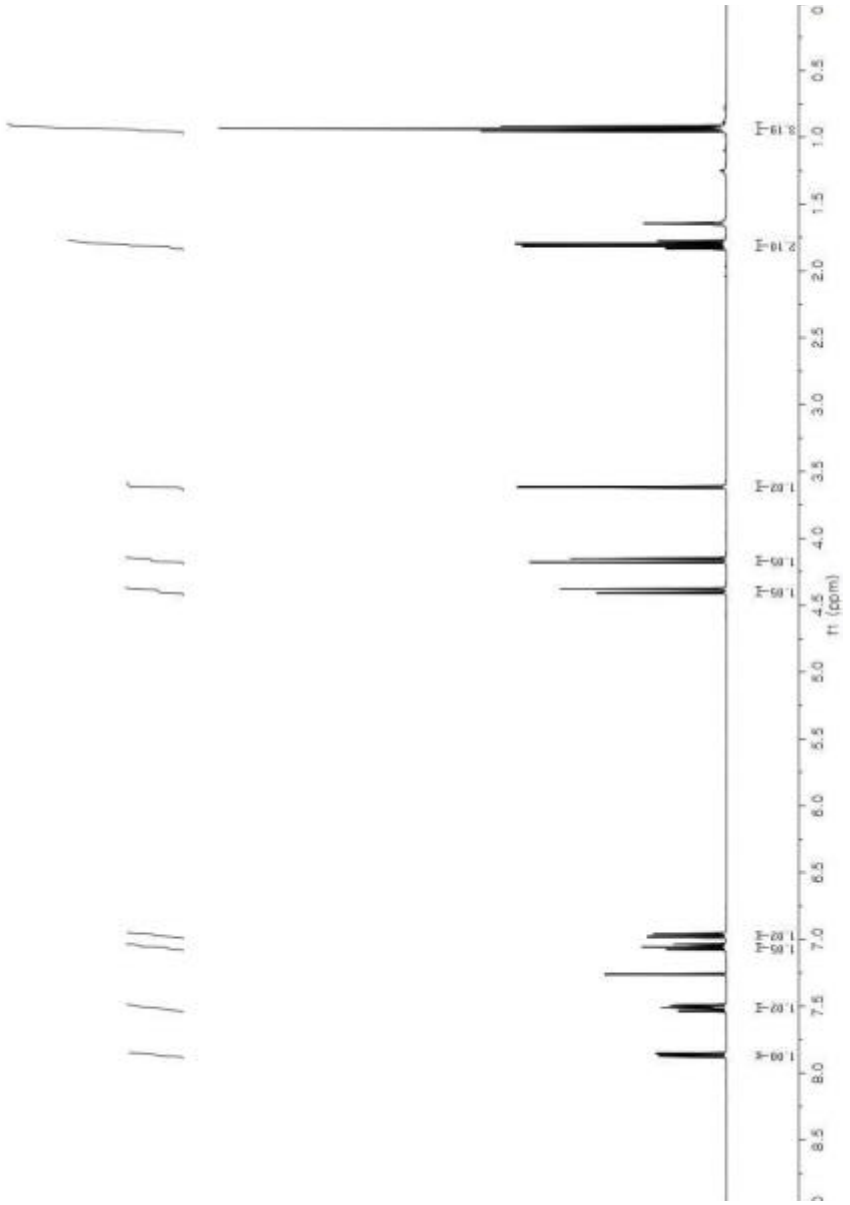
In accordance with Procedure A, H_2-**3.1m** (0.15 mmol, 100 mol%) was reacted with ethylene (15 x 125 mm pressure tube, 0.71 mmol, 480 mol%) in toluene (1.5 M) at 140 °C for a 48 hour period. Flash column chromatography (SiO_2: 2-4% ethyl acetate/hexanes) provided the title compound (17.3 mg, 0.09 mmol) as a yellow oil in 60% yield. NOTE: $Os_3(CO)_{12}$ (2.7 mg, 0.003 mmol, 2 mol%), XPhos (8.5 mg, 0.018 mmol, 12 mol%) and $AdCO_2H$ (2.7 mg, 0.015mmol, 10 mol%).

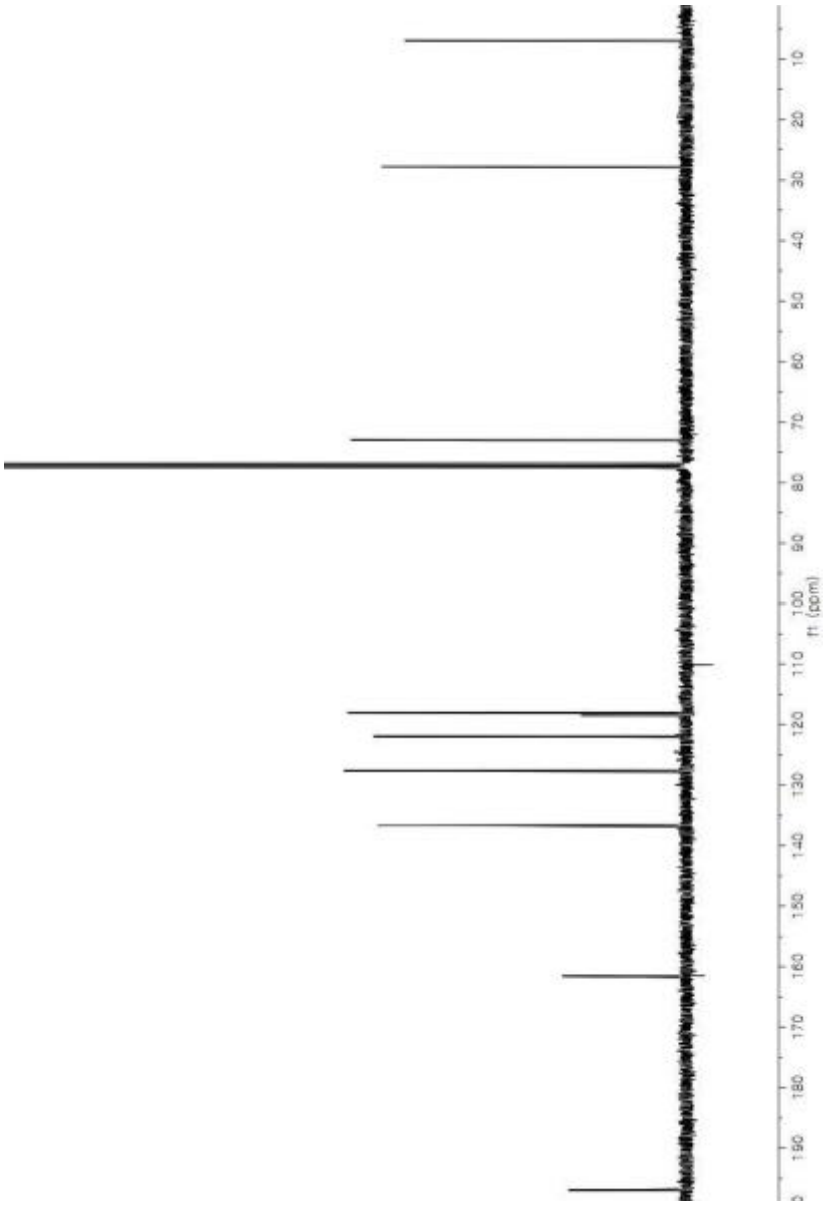
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89–7.85 (m, 1H), 7.51 (ddd, *J* = 8.4, 7.2, 1.8 Hz, 1H), 7.06 (ddd, *J* = 8.0, 7.2, 1.0 Hz, 1H), 6.97 (dd, *J* = 8.4, 0.6 Hz, 1H), 4.39 (d, *J* = 11.3 Hz, 1H), 4.16 (d, *J* = 11.3 Hz, 1H), 3.62 (s, 1H), 1.80 (q, *J* = 7.5 Hz, 2H), 0.94 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 161.5, 136.7, 127.6, 121.9, 118.5, 118.0, 73.1, 72.9, 27.8, 7.0.

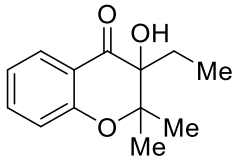
LRMS (CI) Calcd. for $C_{11}H_{12}O_3$, $[M+H]^+$: 193, Found: 193.

FTIR (neat): 3466, 2973, 2936, 1691, 1607.


3.19
2.19
1.02
1.03
1.05
1.02
1.05
1.02
1.00
f1 (ppm)


f1 (ppm)

3-Ethyl-3-hydroxy-2,2-dimethylchroman-4-one (3.3n).



Using ketol

In accordance with Procedure A, **3.1n** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 140 °C for a 40 hour period. Flash column chromatography (SiO_2: 2-4% ether/hexanes) provided the title compound (56.2 mg, 0.26 mmol) as a yellow oil in 85% yield.

Using diol

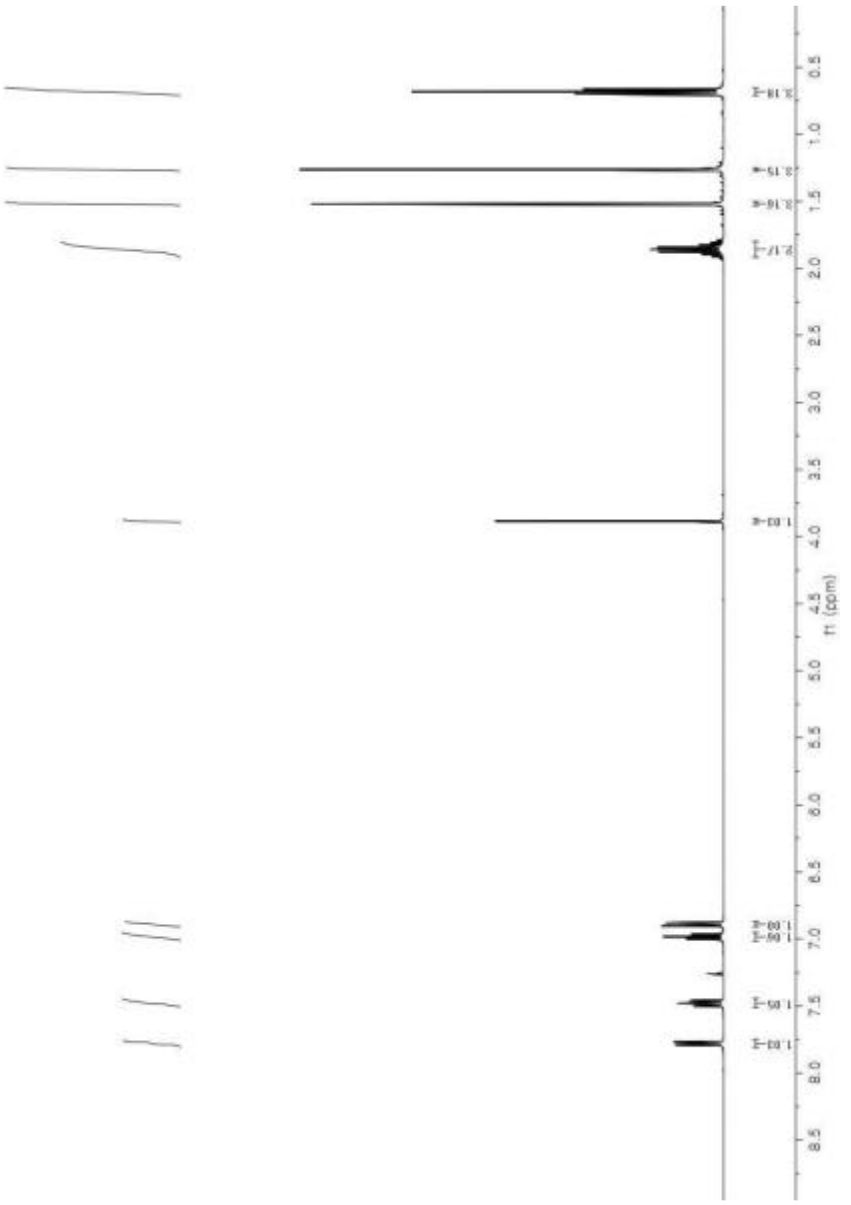
In accordance with Procedure A, H_2-**3.1n** (0.15 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 390 mol%) in toluene (1.5 M) at 140 °C for a 48 hour period. Flash column chromatography (SiO_2: 2-4% ethyl acetate/hexanes) provided the title compound (31.1 mg, 0.14 mmol) as a yellow oil in 94% yield. NOTE: $Os_3(CO)_{12}$ (2.7 mg, 0.003 mmol, 2 mol%), XPhos (8.5 mg, 0.018 mmol, 12 mol%).

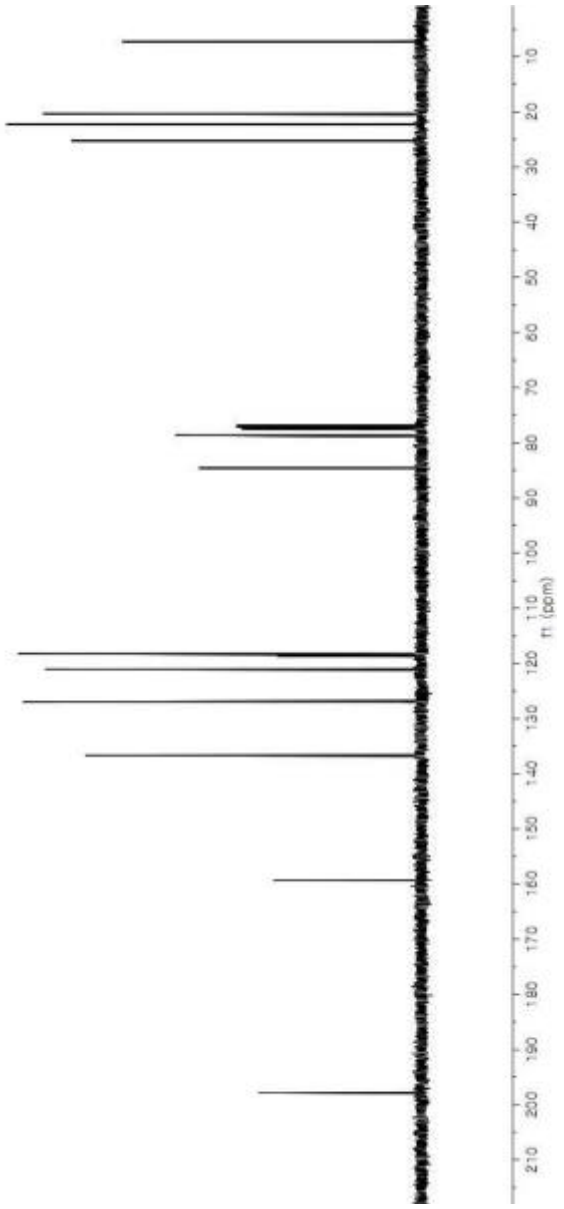
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.48 (ddd, *J* = 8.6, 7.2, 1.8 Hz, 1H), 6.98 (dt, *J* = 12.0, 2.5 Hz, 1H), 6.89 (dd, *J* = 8.4, 0.5 Hz, 1H), 3.89 (s, 1H), 1.92–1.80 (m, 2H), 1.52 (s, 3H), 1.26 (s, 3H), 0.68 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 159.3, 136.7, 126.9, 121.1, 118.7, 118.3, 84.6, 78.7, 25.3, 22.2, 20.4, 7.3.

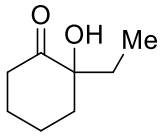
LRMS (ESI) Calcd. for $C_{13}H_{16}O_3$, $[M+Na]^+$: 243, Found: 243.

FTIR (neat): 3484, 2976, 1690.


3.18-H
3.15-H
3.16-H
2.17-H
1.03-H
1.00-H
1.00-H
1.05-H
1.03-H
f1 (ppm)


f1 (ppm)

2-Ethyl-2-hydroxycyclohexan-1-one (3.3o).



Using ketol

In accordance with Procedure A, **3.1o** (0.3 mmol, 100 mol%) was reacted with ethylene (15 x 100 mm pressure tube, 0.58 mmol, 190 mol%) in toluene (2.0 M) at 130 °C for a 48 hour period. Flash column chromatography (SiO_2: 5-10% ether/hexanes) provided the title compound (31.1 mg, 0.22 mmol) as a colorless oil in 73% yield.

Using diol

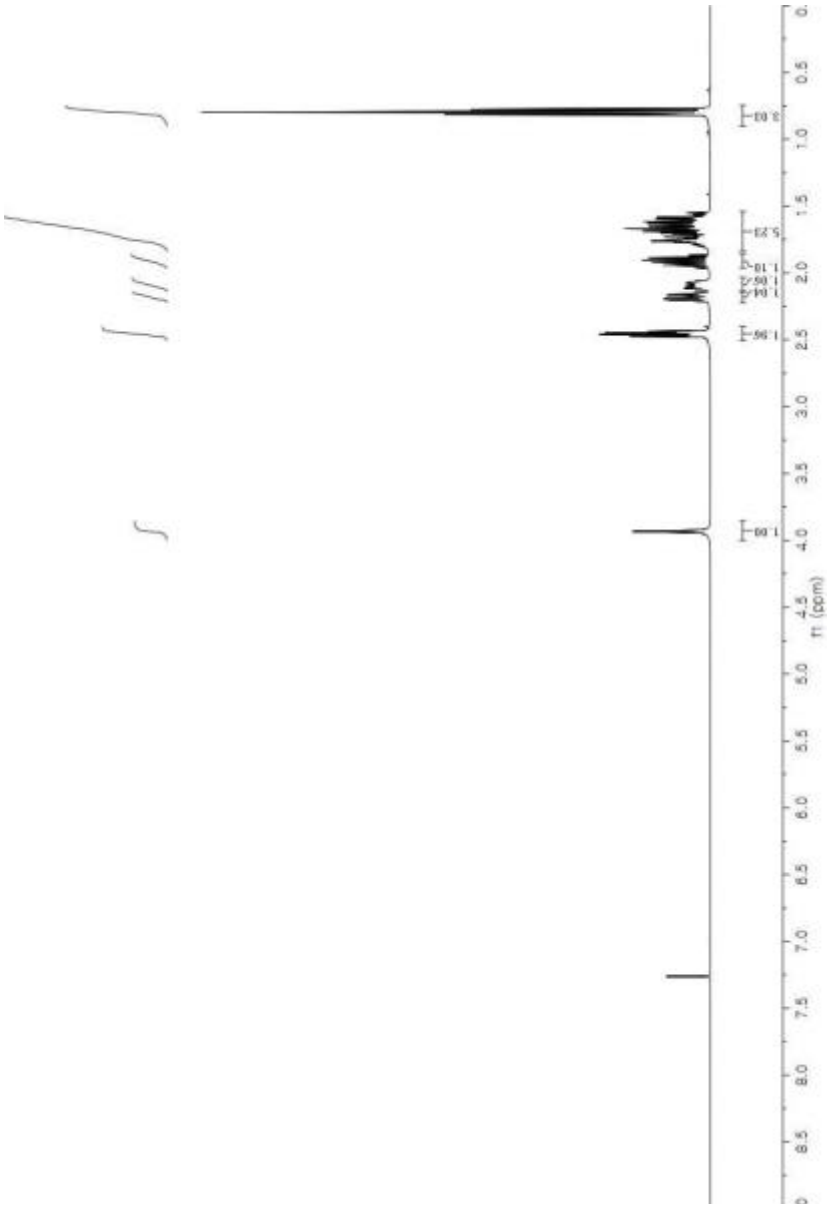
In accordance with Procedure A, H_2-**3.1o** (0.15 mmol, 100 mol%) was reacted with ethylene (15 x 125 mm pressure tube, 0.71 mmol, 480 mol%) in meistylene (2.0 M) at 150 °C for a 48 hour period. Flash column chromatography (SiO_2: 5-10% ether/hexanes) provided the title compound (10.7 mg, 0.15 mmol) as a colorless oil in 50% yield. NOTE: $Os_3(CO)_{12}$ (4.1 mg, 0.0045 mmol, 3 mol%), XPhos (13.2 mg, 0.027 mmol, 18 mol%) and $AdCO_2H$ (4.1 mg, 0.023mmol, 15 mol%).

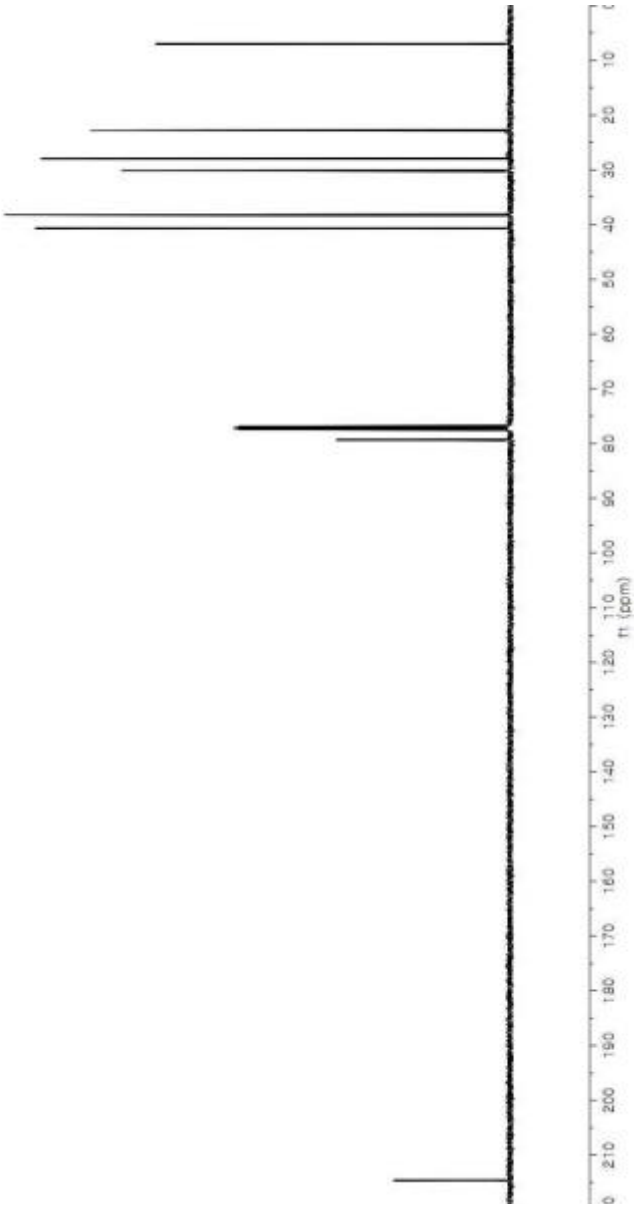
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 1H), 2.51–2.40 (m, 2H), 2.18 (ddd, *J* = 13.1, 5.8, 3.0 Hz, 1H), 2.14–2.03 (m, 1H), 1.91 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.84–1.54 (m, 5H), 0.90–0.75 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 214.6, 79.4, 40.7, 38.2, 30.2, 28.0, 22.9, 7.0.

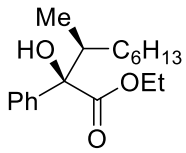
LRMS (ESI) Calcd. for $C_8H_{14}O_2$, $[M+Na]^+$: 165, Found: 165.

FTIR (neat): 3485, 2938, 1707.


f1 (ppm)


f1 (ppm)

Ethyl 2-hydroxy-3-methyl-2-phenylnonanoate (3.3p).



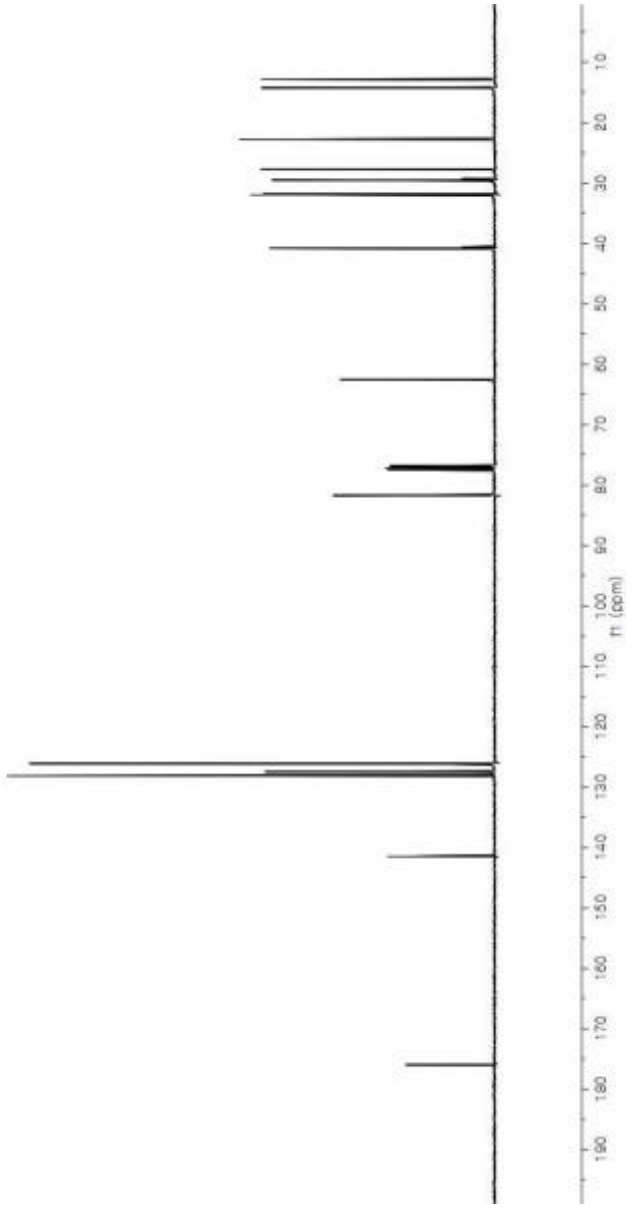
In accordance with Procedure B, **3.1a** (0.2 mmol, 100 mol%) was reacted with 1-octene (13 x 100 mm pressure tube, 0.15 mL, 1.0 mmol, 500 mol%) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 2% ether/hexanes) provided the title compound (31.1 mg, 0.22 mmol, *d.r.* = 5:1) as a colorless oil in 62% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major) 7.67–7.62 (m, 2H), 7.37–7.30 (m, 2H), 7.29–7.24 (m, 1H), 4.33–4.13 (m, 2H), 3.68 (d, *J* = 0.6 Hz, 1H), 2.47–2.35 (m, 1H), 1.51–1.16 (m, 13H), 0.90 (dd, *J* = 8.9, 4.9 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H). (minor) 7.67–7.62 (m, 2H), 7.37–7.30 (m, 2H), 7.29–7.24 (m, 1H), 4.33–4.13 (m, 2H), 3.74 (d, *J* = 0.6 Hz, 1H), 2.47–2.35 (m, 1H), 1.51–1.16 (m, 13H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.82 (t, *J* = 7.1 Hz, 3H).

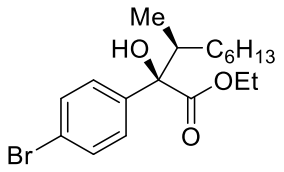
^{13}C NMR (100 MHz, $CDCl_3$): δ (major) 176.0, 141.5, 128.1, 127.5, 126.1, 81.7, 62.5, 40.8, 31.9, 31.8, 29.5, 27.7, 22.8, 14.3, 14.2, 12.8. (minor) 175.9, 141.3, 128.1, 127.5, 126.2, 81.6, 62.6, 40.6, 31.9, 29.6, 29.3, 27.6, 22.7, 14.2, 14.1, 12.8.

LRMS (ESI) Calcd. for $C_{18}H_{28}O_3$, $[M+Na]^+$: 315, Found: 315.

FTIR (neat): 3514, 2928, 2857, 1721.


f1 (ppm)

Ethyl 2-(4-bromophenyl)-2-hydroxy-3-methylnonanoate (3.3qb).



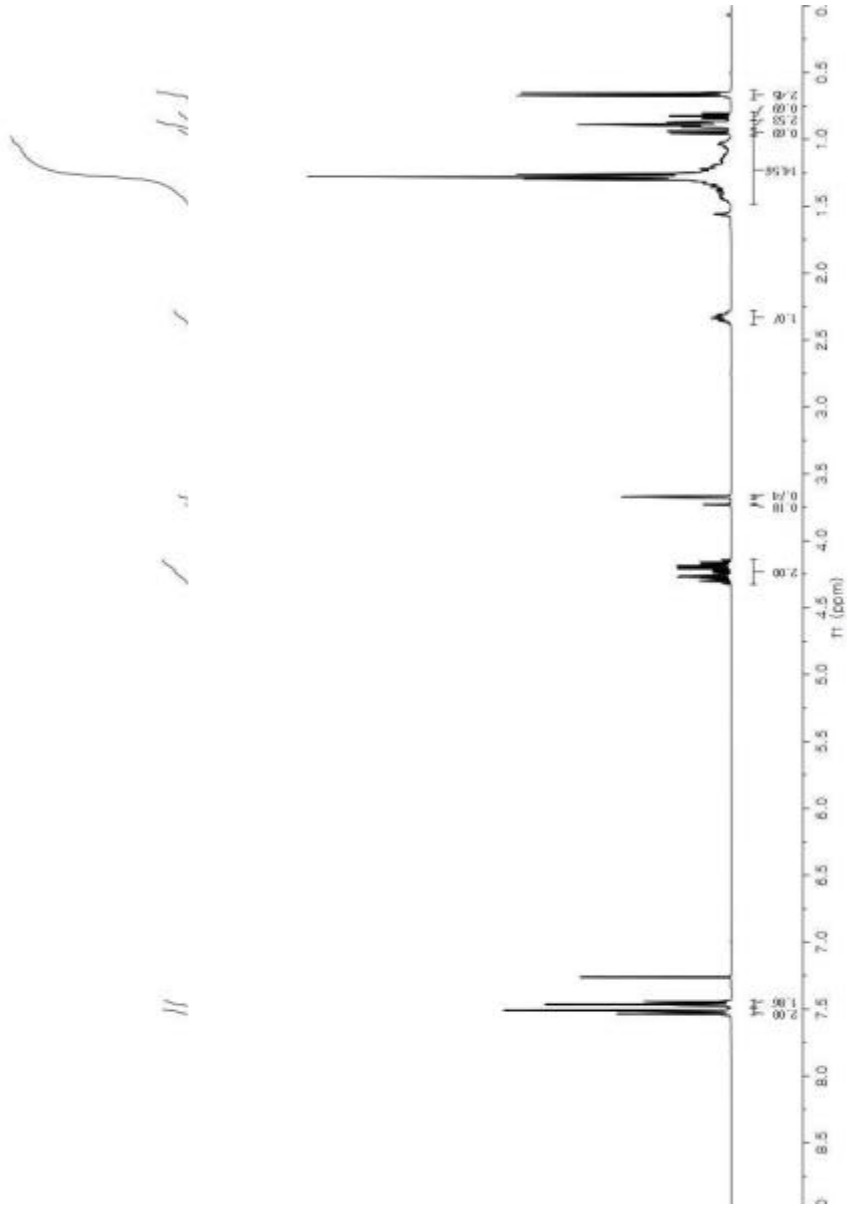
In accordance with Procedure B, **3.1b** (0.2 mmol, 100 mol%) was reacted with 1-octene (13 x 100 mm pressure tube, 0.15 mL, 1.0 mmol, 500 mol%) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 20-35% dichloromethane/hexanes) provided the title compound (45.4 mg, 0.12 mmol, *d.r.* = 4:1) as a colorless oil in 61% yield.

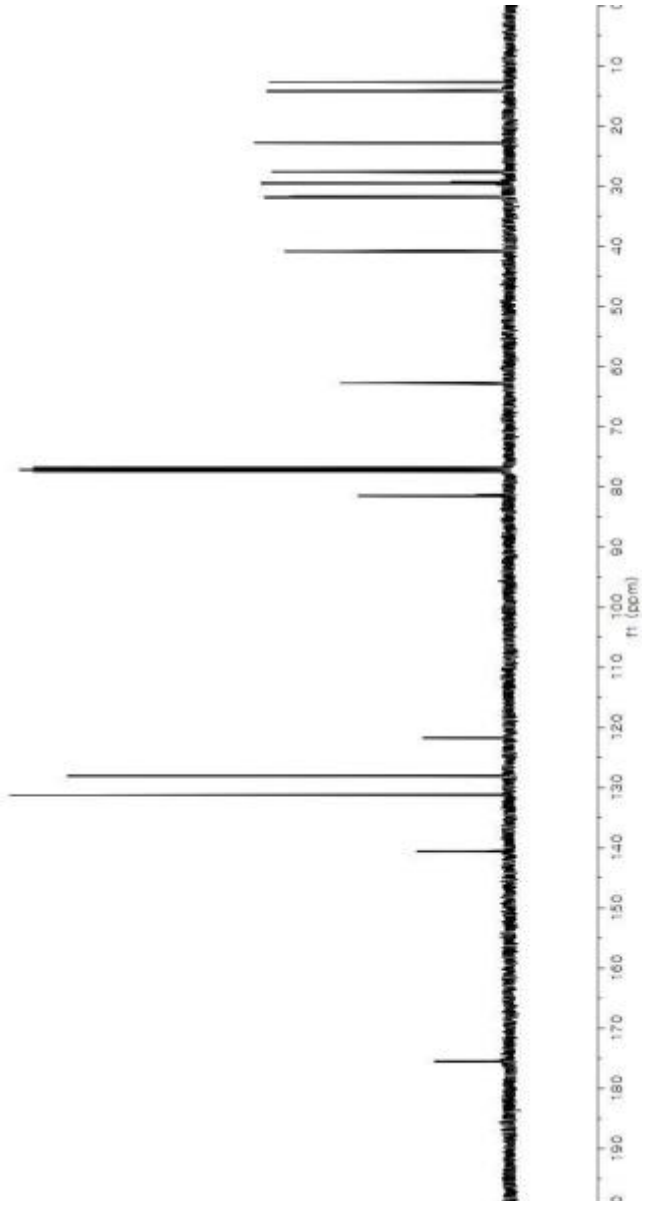
^{1}H NMR (400 MHz, $CDCl_3$): δ (major) 7.54–7.50 (m, 2H), 7.48–7.43 (m, 2H), 4.33–4.14 (m, 2H), 3.67 (s, 1H), 2.38–2.28 (m, 1H), 1.48–0.97 (m, 13H), 0.89 (d, J = 6.9 Hz, 3H), 0.66 (d, J = 6.8 Hz, 3H). (minor) 7.54–7.50 (m, 2H), 7.48–7.43 (m, 2H), 4.33–4.14 (m, 2H), 3.73 (s, 1H), 2.38–2.28 (m, 1H), 1.48–0.97 (m, 13H), 0.95 (d, J = 6.6 Hz, 3H), 0.83 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) 175.5, 140.6, 131.3, 128.1, 121.7, 81.5, 62.8, 40.9, 31.9, 31.7, 29.5, 27.6, 22.8, 14.3, 14.2, 12.8. (minor) 175.4, 140.6, 131.3, 128.1, 121.7, 81.4, 62.9, 40.7, 31.9, 29.6, 29.3, 27.6, 22.7, 14.2, 14.1, 12.8.

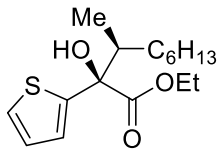
LRMS (ESI) Calcd. for $C_{18}H_{27}BrO_3$, $[M+Na]^+$: 393, Found: 393.

FTIR (neat): 3507, 2927, 2856, 1723.




f1 (ppm)

Ethyl 2-hydroxy-3-methyl-2-(thiophen-2-yl)nonanoate (3.3r).



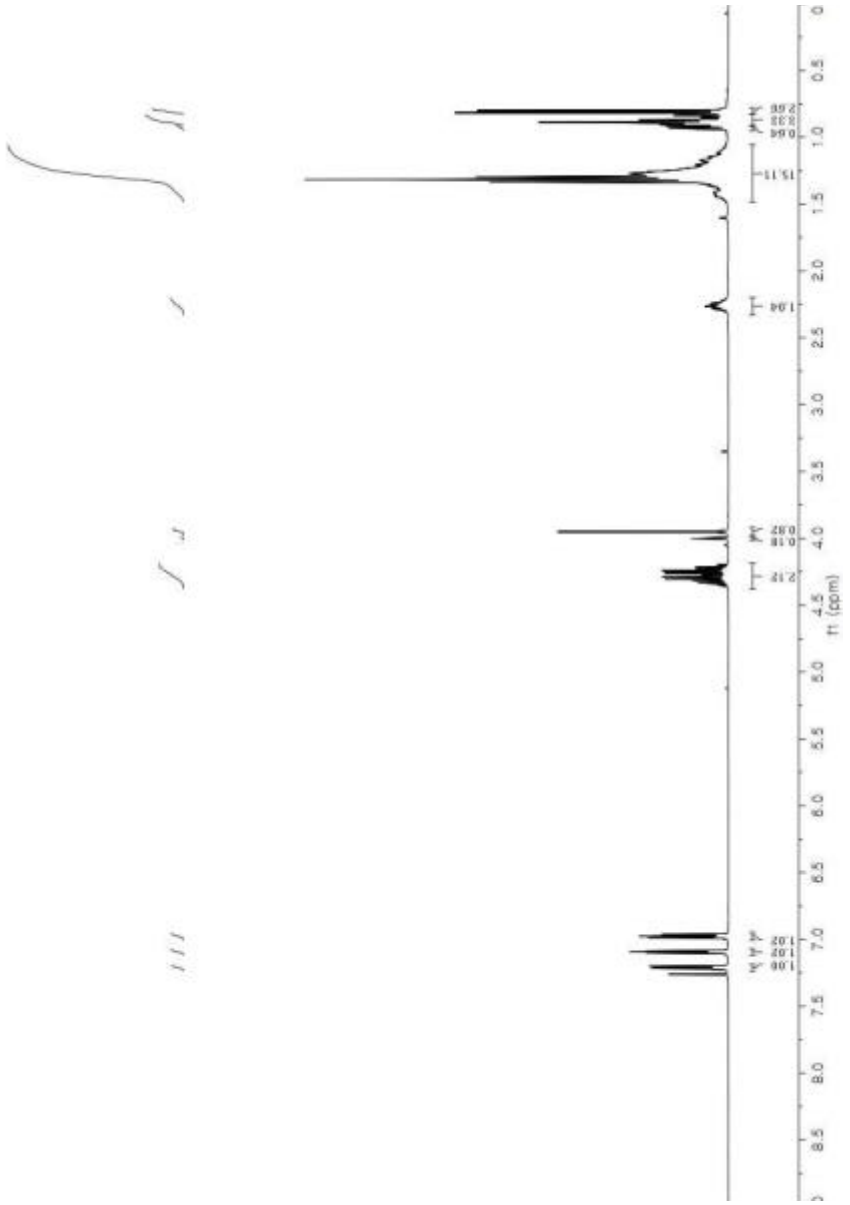
In accordance with Procedure B, **3.1i** (0.2 mmol, 100 mol%) was reacted with 1-octene (13 x 100 mm pressure tube, 0.15 mL, 1.0 mmol, 500 mol%) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 20-40% dichloromethane/hexanes) provided the title compound (47.8 mg, 0.16 mmol, *d.r.* = 5:1) as a colorless oil in 80% yield.

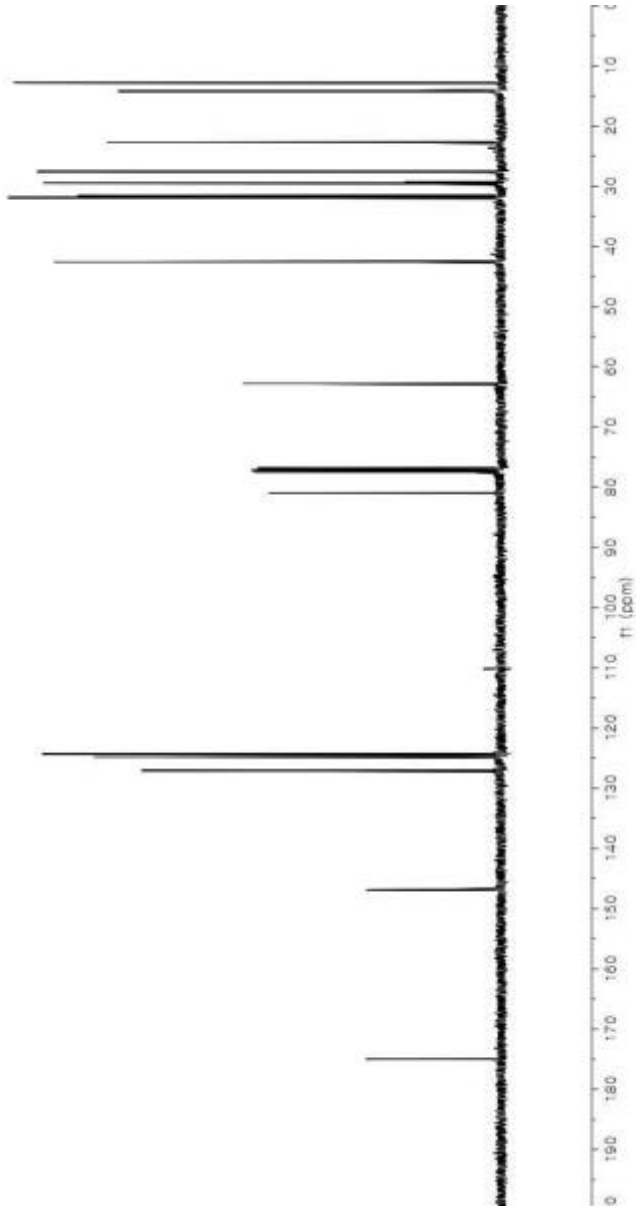
^{1}H NMR (400 MHz, $CDCl_3$): δ (major) 7.21 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.09 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.98 (dd, *J* = 5.2, 3.6 Hz, 1H), 4.38–4.19 (m, 2H), 3.95 (d, *J* = 0.5 Hz, 1H), 2.33–2.20 (m, 1H), 1.48–1.05 (m, 14H), 0.91–0.83 (m, 2H), 0.81 (d, *J* = 6.8 Hz, 3H). (minor) 7.22 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.09 (dd, *J* = 3.6, 1.2 Hz, 1H), 6.99–6.97 (m, 1H), 4.38–4.19 (m, 2H), 4.00 (d, *J* = 0.5 Hz, 1H), 2.33–2.20 (m, 1H), 1.48–1.05 (m, 14H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.91–0.83 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) 175.0, 146.9, 127.1, 124.8, 124.3, 81.0, 62.8, 42.6, 31.9, 31.6, 29.5, 27.6, 22.8, 14.22, 14.15, 12.8. (minor) 174.9, 146.7, 127.1, 124.9, 124.4, 80.9, 62.9, 42.5, 31.9, 29.6, 29.4, 27.7, 22.7, 14.2, 14.0, 12.8.

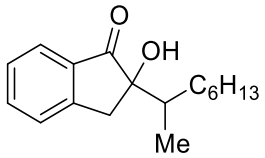
LRMS (ESI) Calcd. for $C_{16}H_{26}O_3S$, $[M+Na]^+$: 321, Found: 321.

FTIR (neat): 3502, 2929, 2857, 1725.


f1 (ppm)


f1 (ppm)

2-Hydroxy-2-(octan-2-yl)-2,3-dihydro-1H-inden-1-one (3.3s).



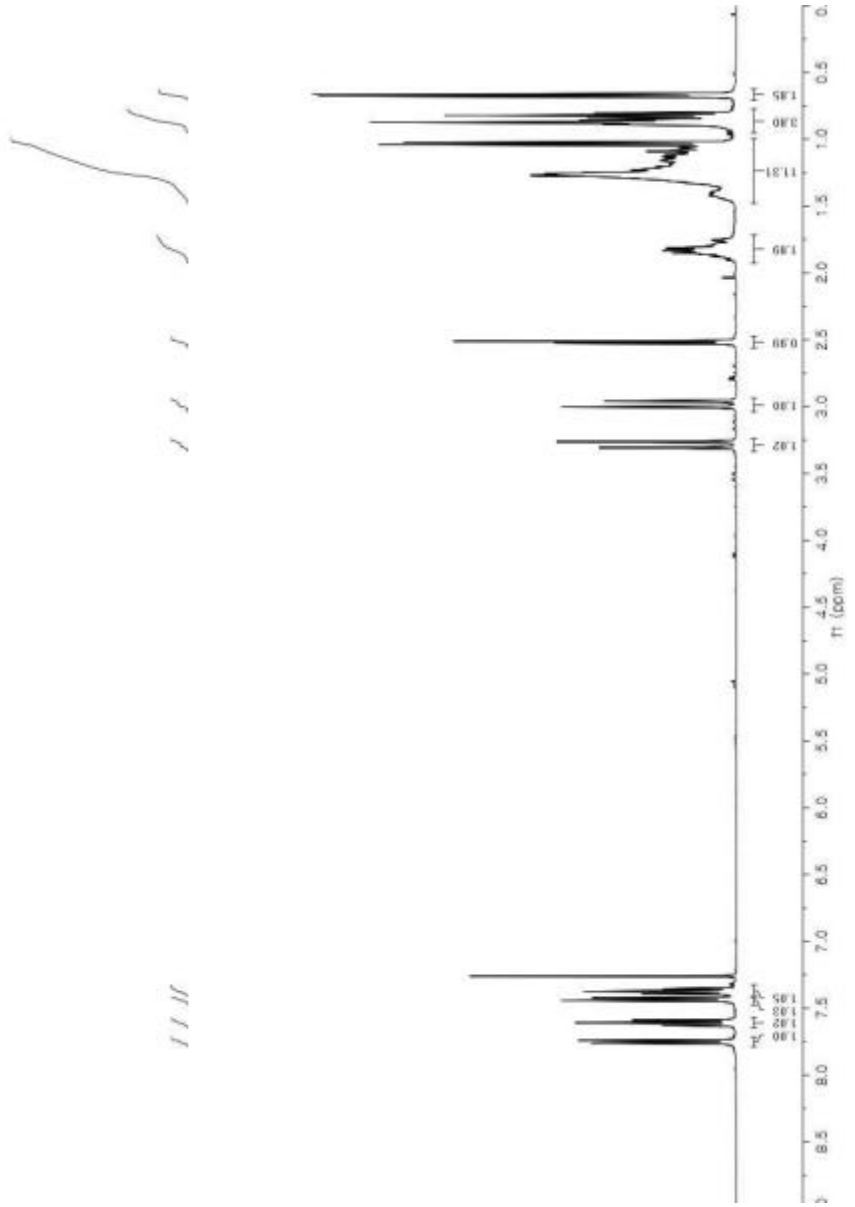
In accordance with Procedure B, **3.1j** (0.2 mmol, 100 mol%) was reacted with 1-octene (13 x 100 mm pressure tube, 0.15 mL, 1.0 mmol, 500 mol%) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 2-3% ether/hexanes) provided the title compound (44.3 mg, 0.17 mmol, *d.r.* = 1:1) as a colorless oil in 85% yield.

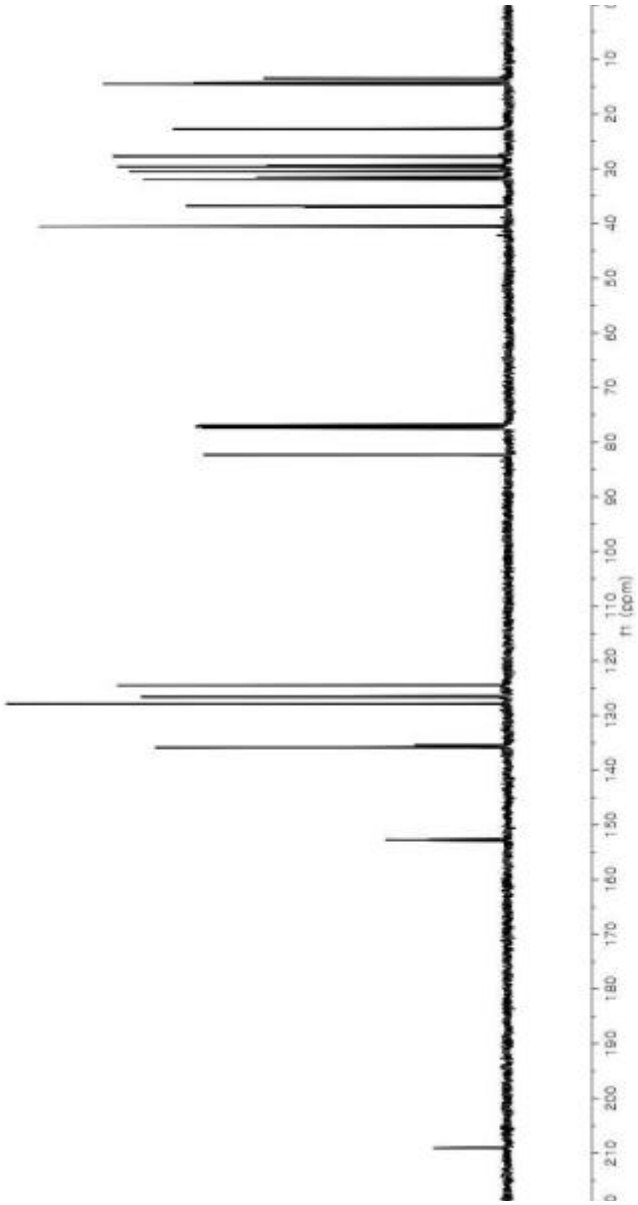
^{1}H NMR (400 MHz, $CDCl_3$): δ (A) 7.75 (d, *J* = 7.7 Hz, 1H), 7.61 (dd, *J* = 10.8, 4.1 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.37 (dd, *J* = 7.5, 7.5 Hz, 1H), 3.28 (d, *J* = 17.4 Hz, 1H), 2.98 (d, *J* = 17.4 Hz, 1H), 2.51 (s, 1H), 1.93–1.72 (m, 15H), 1.48–0.99 (m, 9.5H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.67 (d, *J* = 6.9 Hz, 3H). (B) 7.75 (d, *J* = 7.7 Hz, 1H), 7.61 (dd, *J* = 10.8, 4.1 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.37 (dd, *J* = 7.5 Hz, 7.5 Hz, 1H), 3.28 (d, *J* = 17.4 Hz, 1H), 2.98 (d, *J* = 17.4 Hz, 1H), 2.53 (s, 1H), 1.93–1.72 (m, 1.5 H), 1.48–0.99 (m, 12.5H), 0.82 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (A) 209.1, 152.8, 135.8, 135.4, 127.8, 126.6, 124.5, 82.3, 40.6, 36.8, 32.0, 30.5, 29.6, 27.8, 22.8, 14.5, 13.5. (B) 209.0, 152.6, 135.8, 135.5, 127.8, 126.7, 124.5, 82.3, 40.6, 37.1, 31.9, 31.5, 29.4, 27.7, 22.7, 14.22, 14.16.

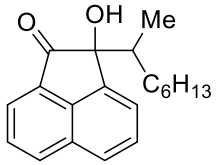
LRMS (ESI) Calcd. for $C_{17}H_{24}O_2$, $[M+Na]^+$: 283, Found: 283.

FTIR (neat): 3447, 2926, 1709.




f1 (ppm)

2-Hydroxy-2-(octan-2-yl)acenaphthylen-1(2H)-one (3.3t).



(Using dihydro-1k)

In accordance with Procedure B, *dihydro*-**3.1k** (0.2 mmol, 100 mol%) was reacted with 1-octene (13 x 100 mm pressure tube, 0.15 mL, 1.0 mmol, 500 mol%) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 5-7% ethyl acetate/hexanes) provided the title compound (41.5 mg, 0.14 mmol, *d.r.* = 2:1) as a light green solid in 70% yield.

(Using 1k)

In accordance with Procedure B, **3.1k** (0.2 mmol, 100 mol%) was reacted with 1-octene (13 x 100 mm pressure tube, 0.15 mL, 1.0 mmol, 500 mol%) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 5-7% ethyl acetate/hexanes) provided the title compound (56.3 mg, 0.19 mmol, *d.r.* = 2:1) as a light green solid in 95% yield.

(Using dehydro-1k)

In accordance with Procedure B, *dehydro*-**3.1k** (0.2 mmol, 100 mol%) was reacted with 1-octene (13 x 100 mm pressure tube, 0.15 mL, 1.0 mmol, 500 mol%) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 5-7% ethyl acetate/hexanes) provided the title compound (40.3 mg, 0.14 mmol, *d.r.* = 2:1) as a light green solid in 68% yield. NOTE: The reaction was conducted in the presence of 1,3-butane diol (36.0 mg, 0.4 mmol, 200 mol%)

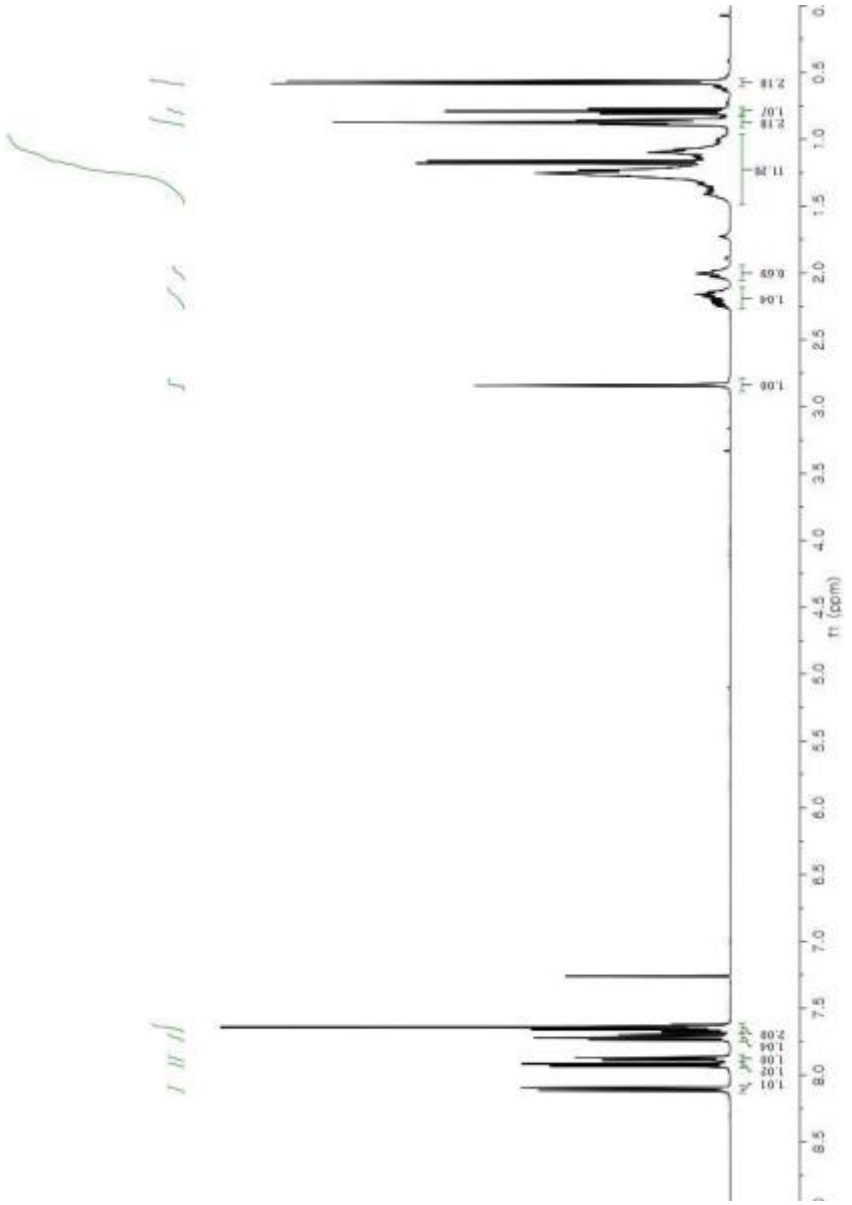
^{1}H NMR (400 MHz, $CDCl_3$): δ (major) 8.11 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.92 (ddd, *J* = 4.0, 2.0, 2.0 Hz, 1H), 7.90–7.85 (m, 1H), 7.72 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.68–7.61 (m, 2H), 2.84 (d, *J* = 2.4 Hz, 1H), 2.27–1.94 (m, 1H), 1.49–0.96 (m, 10H), 0.91–0.83 (m, 3H), 0.58 (t, *J* = 6.2 Hz, 3H). (minor) 8.11 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.92 (ddd, *J* = 4.0, 2.0, 2.0 Hz, 1H), 7.90–7.85 (m, 1H), 7.72 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H), 7.68–7.61 (m, 2H), 2.84 (d, *J* = 2.4 Hz, 1H), 2.27–1.94 (m, 1H), 1.49–0.96 (m, 13H), 0.79 (t, *J* = 7.1 Hz, 3H).

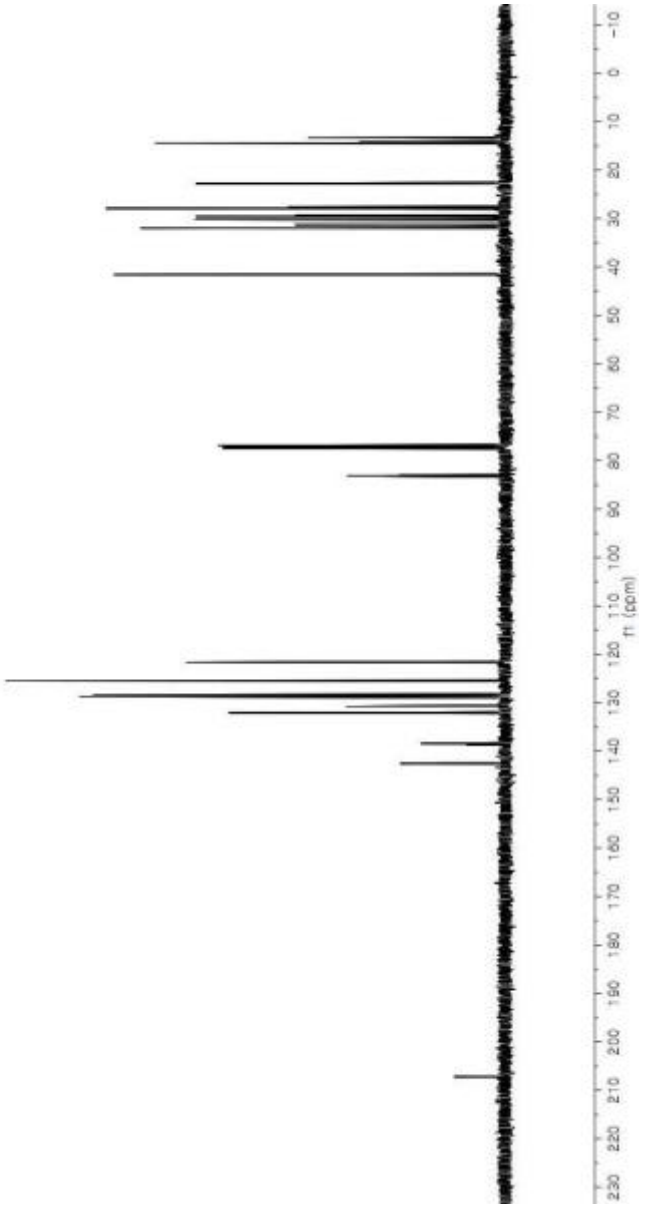
^{13}C NMR (100 MHz, $CDCl_3$): δ (major) 207.2, 142.5, 138.4, 132.01, 131.99, 130.7, 128.7, 128.3, 125.4, 121.7, 121.6, 83.1, 41.6, 32.0, 30.2, 29.6, 27.9, 22.8, 14.4, 14.2. (minor) 207.2, 142.4, 138.7, 132.0, 131.9, 130.8, 128.7, 128.3, 125.4, 121.6, 121.4, 82.9, 41.4, 31.8, 31.3, 29.2, 27.5, 22.6, 14.1, 13.3.

LRMS (ESI) Calcd. for $C_{20}H_{24}O_2$, $[M+Na]^+$: 319, Found: 319.

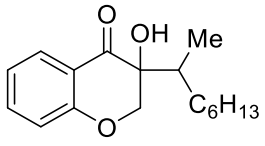
FTIR (neat): 3423, 2924, 1708.

MP: 79.8–81.1 °C.


2.18
1.07
2.18
11.28
0.69
1.04
1.00
1.01
1.02
1.00
1.04
2.08
f1 (ppm)


f1 (ppm)

3-Hydroxy-3-(octan-2-yl)chroman-4-one (3.3u).



In accordance with Procedure B, **3.1m** (0.2 mmol, 100 mol%) was reacted with 1-octene (13 x 100 mm pressure tube, 0.15 mL, 1.0 mmol, 500 mol%) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 2-3% ether/hexanes) provided the title compound (34.8 mg, 0.13 mmol, *d.r.* = 1:1) as a pale yellow solid in 63% yield.

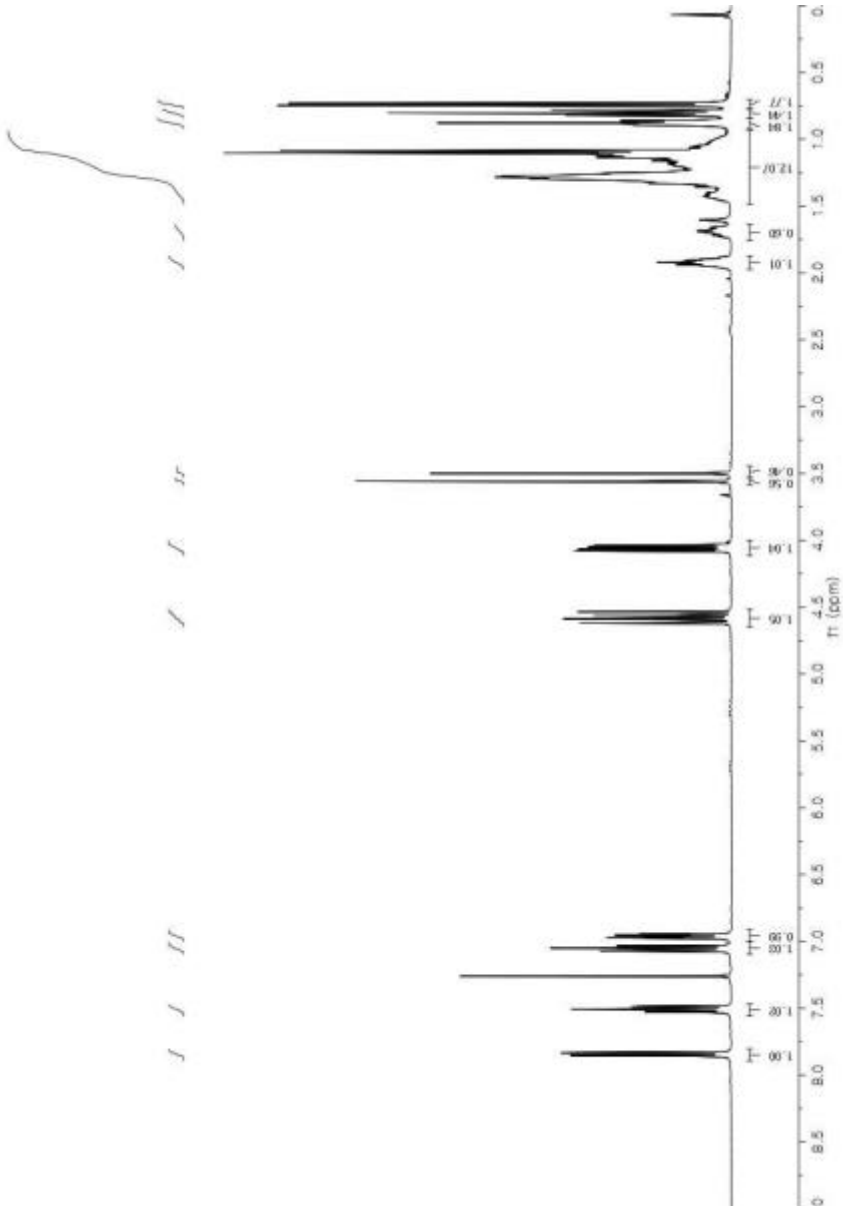
^{1}H NMR (400 MHz, $CDCl_3$): δ (A) 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56–7.47 (m, 1H), 7.05 (ddd, *J* = 8.2, 1.9, 1.0 Hz, 1H), 6.96 (ddd, *J* = 8.4, 3.0, 0.6 Hz, 1H), 4.58 (dd, *J* = 21.0, 11.7 Hz, 1H), 4.06 (dd, *J* = 11.7, 5.6 Hz, 1H), 3.56 (s, 1H), 1.97–1.87 (m, 1H), 1.76–1.64 (m, 0.5H), 1.49–0.94 (m, 12.5H), 0.88 (dd, *J* = 8.4, 5.0 Hz, 3H). (B) 7.84 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56–7.47 (m, 1H), 7.05 (ddd, *J* = 8.2, 1.9, 1.0 Hz, 1H), 6.96 (ddd, *J* = 8.4, 3.0, 0.6 Hz, 1H), 4.58 (dd, *J* = 21.0, 11.7 Hz, 1H), 1.76–1.64 (m, 0.5H), 1.49–0.94 (m, 9.5H), 0.80 (t, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H).

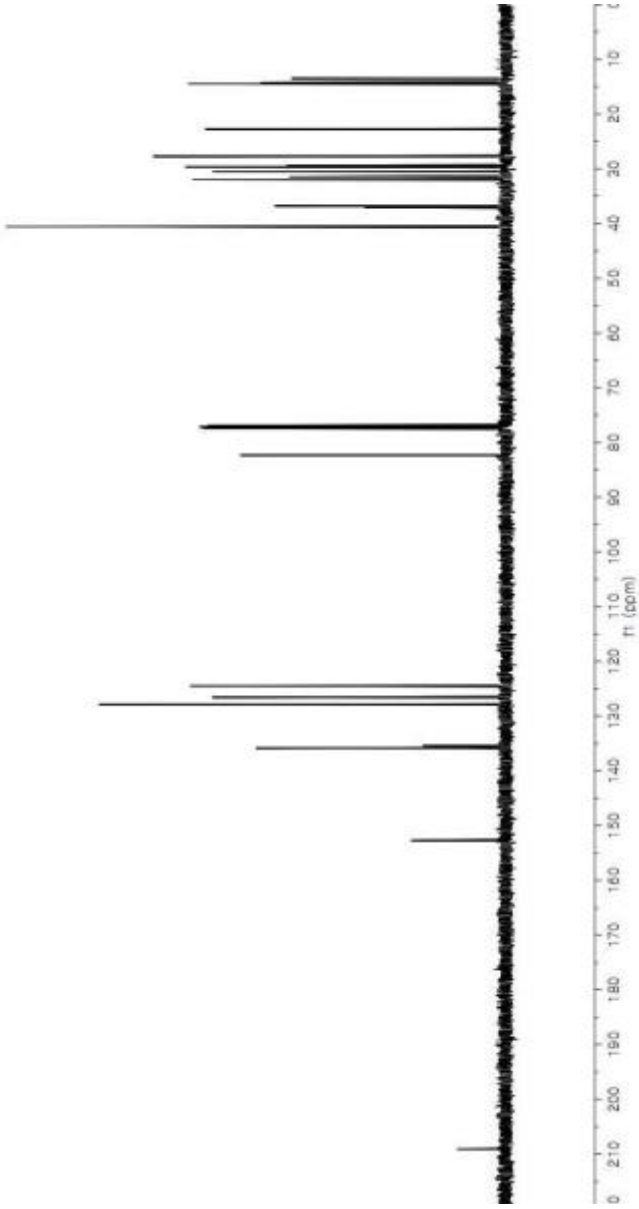
^{13}C NMR (100 MHz, $CDCl_3$): δ (A) 209.1, 152.8, 135.8, 135.4, 127.8, 126.6, 124.5, 82.3, 40.6, 36.8, 32.0, 31.5, 29.6, 27.7, 22.8, 14.5, 14.2. (B) 209.1, 152.6, 135.8, 135.4, 127.8, 126.7, 124.5, 82.3, 40.6, 37.1, 31.9, 30.5, 29.4, 27.7, 22.7, 14.2, 13.5.

LRMS (ESI) Calcd. for $C_{17}H_{24}O_3$, $[M+Na]^+$: 299, Found: 299.

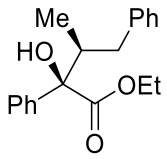
FTIR (neat): 3453, 2927, 1684.

MP: 67.8–68.0 ºC.




f1 (ppm)

Ethyl 2-hydroxy-3-methyl-2,4-diphenylbutanoate (3.3v).



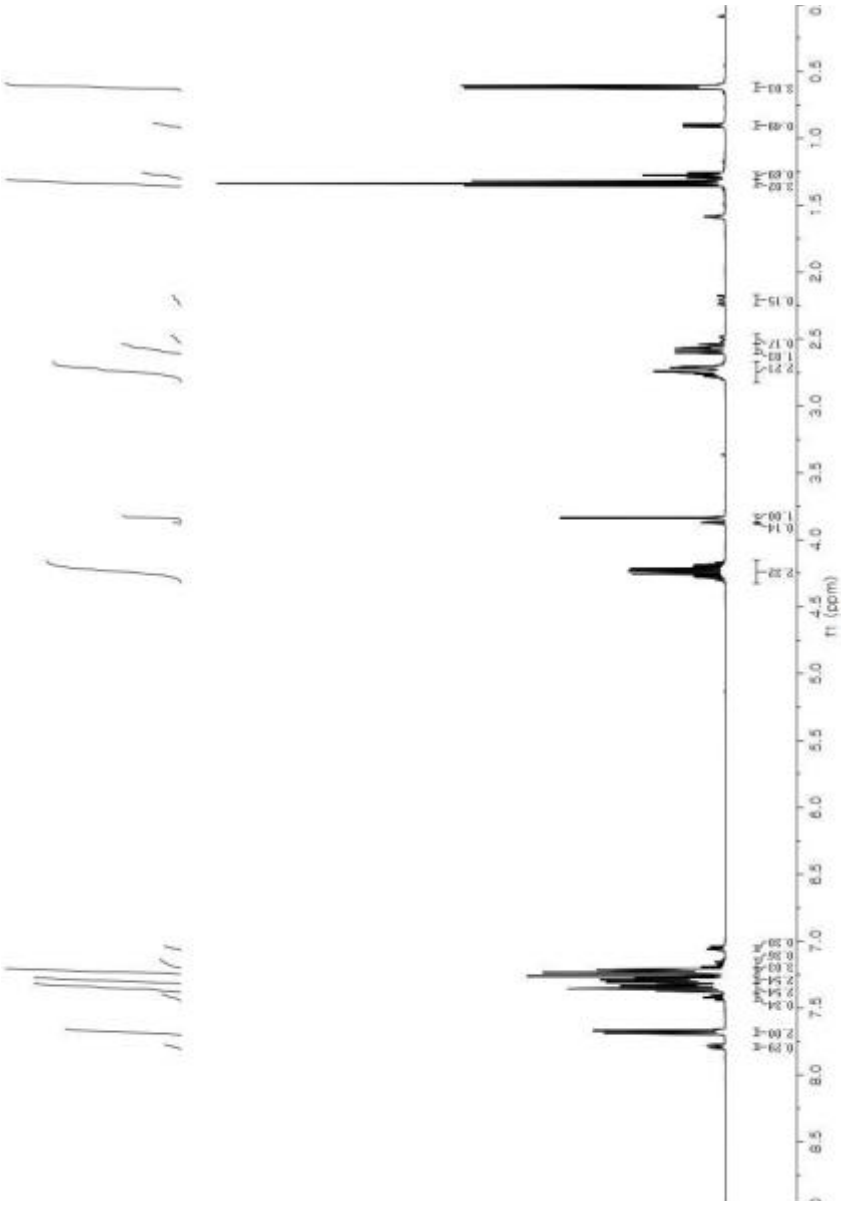
In accordance with Procedure B, **3.1a** (0.2 mmol, 100 mol%) was reacted with **3.2c** (13 x 100 mm pressure tube, 0.13 mL, 1.0 mmol, 500 mol%) in toluene (2.0 M) at 130 °C for a 40 hour period. Flash column chromatography (SiO_2: 30-60% dichloromethane/hexanes) provided the title compound (34.6 mg, 0.11 mmol, *d.r.* = 5:1) as colorless oil in 58% yield. NOTE: $AdCO_2H$ (30 mol%)

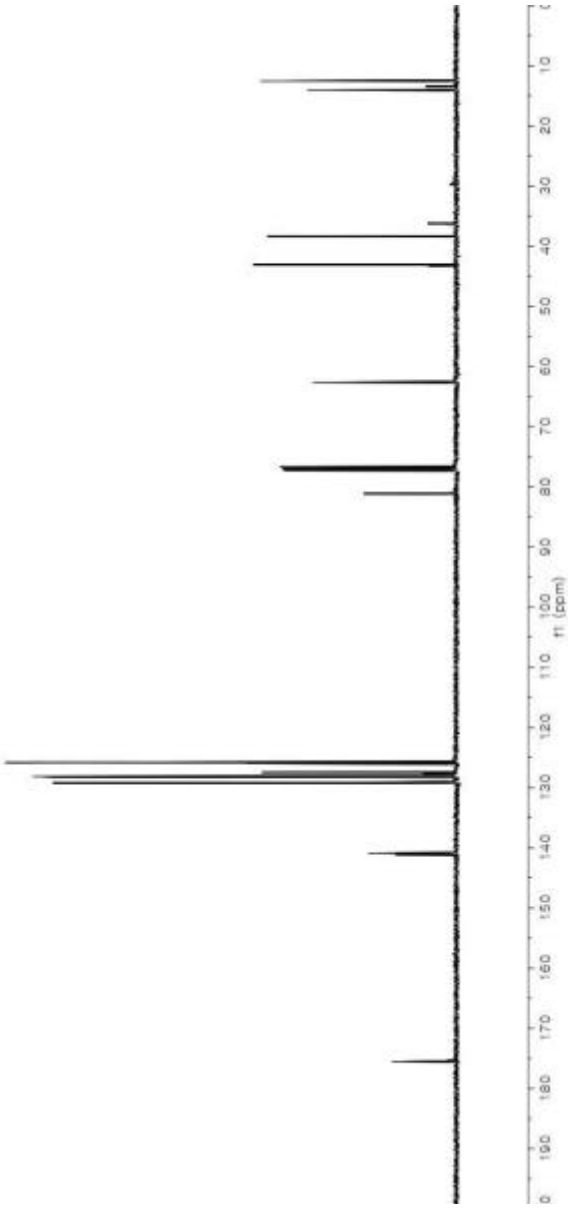
^{1}H NMR (400 MHz, $CDCl_3$): δ (major) 7.71–7.65 (m, 2H), 7.38–7.26 (m, 5H), 7.22 (d, *J* = 7.3 Hz, 3H), 4.33–4.15 (m, 2H), 3.84 (d, *J* = 0.5 Hz, 1H), 2.82–2.67 (m, 2H), 2.57 (dd, *J* = 13.4, 10.5 Hz 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.62 (t, *J* = 6.8 Hz, 3H). (minor) 7.81–7.77 (m, 2H), 7.42 (dd, *J* = 10.5, 4.9 Hz, 2H), 7.38–7.26 (m, 2H), 7.18 (dd, *J* = 11.2, 4.3 Hz, 2H), 7.05 (d, *J* = 7.1 Hz, 2H), 4.33–4.15 (m, 2H), 3.87 (d, *J* = 0.6 Hz, 1H), 2.82–2.67 (m, 1H), 2.50 (d, *J* = 13.7 Hz, 1H), 2.21 (dd, *J* = 13.6 Hz, 11.6 Hz, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) 175.8, 141.3, 141.0, 129.4, 128.4, 128.3, 127.6, 126.1, 126.0, 81.3, 62.8, 43.2, 38.6, 14.3, 12.7. (minor) 175.5, 141.4, 141.1, 129.2, 128.4, 128.3, 127.8, 126.2, 125.9, 81.2, 62.8, 43.4, 36.4, 14.2, 13.6.

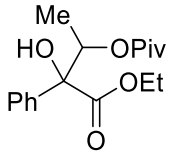
LRMS (ESI) Calcd. for $C_{19}H_{22}O_3$, $[M+Na]^+$: 321, Found: 321.

FTIR (neat): 3505, 2976, 2361, 2342, 1715.




f1 (ppm)

Ethyl 2-hydroxy-2-phenyl-3-(pivaloyloxy)butanoate (3.3w).



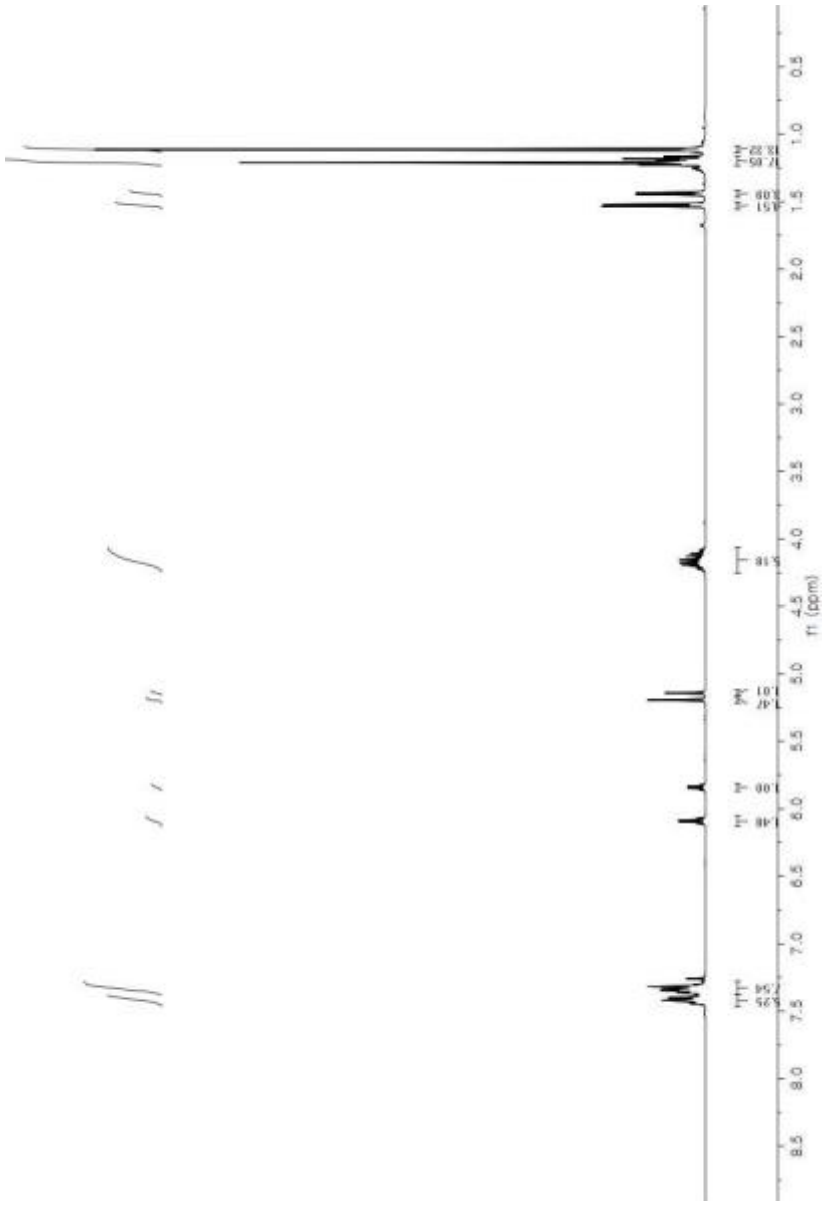
In accordance with Procedure B, **3.1a** (0.2 mmol, 100 mol%) was reacted with **3.2d** (13 x 100 mm pressure tube, 0.09 mL, 0.6 mmol, 300 mol%) in toluene (2.0 M) at 130 °C for a 24 hour period. Flash column chromatography (SiO_2: 2-4% ethyl acetate/hexanes) provided the title compound (51.8 mg, 0.25 mmol, *d.r.* = 1.5:1) as a pale yellow oil in 84% yield. NOTE: XPhos and $AdCO_2H$ was omitted.

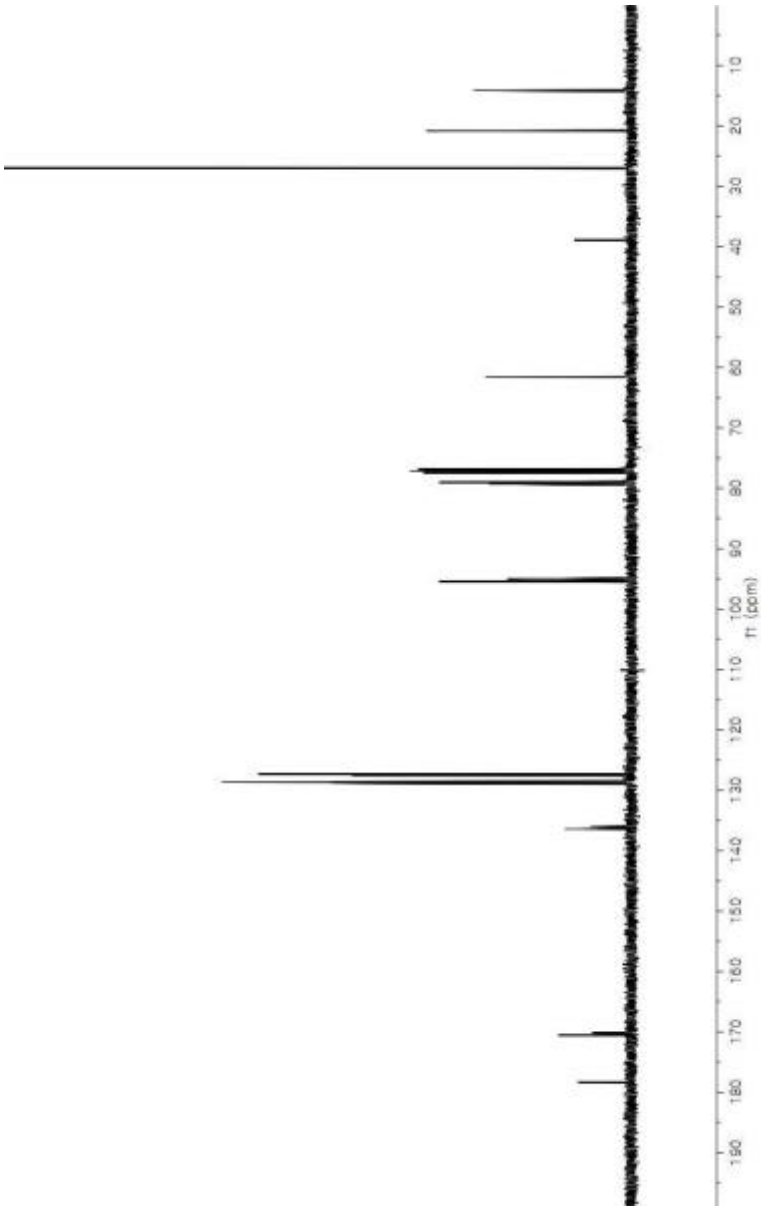
^{1}H NMR (400 MHz, $CDCl_3$): δ (major) 7.47–7.28 (m, 5H), 6.09 (q, *J* = 5.2 Hz, 1H), 5.19 (s, 1H), 4.25–4.06 (m, 2H), 1.53 (d, *J* = 5.2 Hz, 3H), 1.23–1.17 (m, 3H), 1.11 (s, 9H). (minor) 7.47–7.28 (m, 5H), 5.84 (q, *J* = 5.2 Hz, 1H), 5.14 (s, 1H), 4.25–4.06 (m, 2H), 1.44 (d, *J* = 5.3 Hz, 3H), 1.23–1.17 (m, 3H), 1.21 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) 178.3. 170.6. 136.4. 128.7. 128.6. 127.3. 95.5. 79.0. 61.5. 38.9. 27.0. 20.9. 14.2. (minor) 178.3, 170.1, 136.0, 129.0, 128.8, 127.5, 95.0, 79.3, 61.4, 39.0, 27.1, 20.8, 14.1.

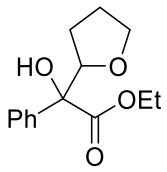
LRMS (ESI) Calcd. for $C_{17}H_{24}O_5$, $[M+Na]^+$: 331, Found: 331.

FTIR (neat): 2979, 1789, 1174.


f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

Ethyl 2-hydroxy-2-phenyl-2-(tetrahydrofuran-2-yl)acetate (3.3x).



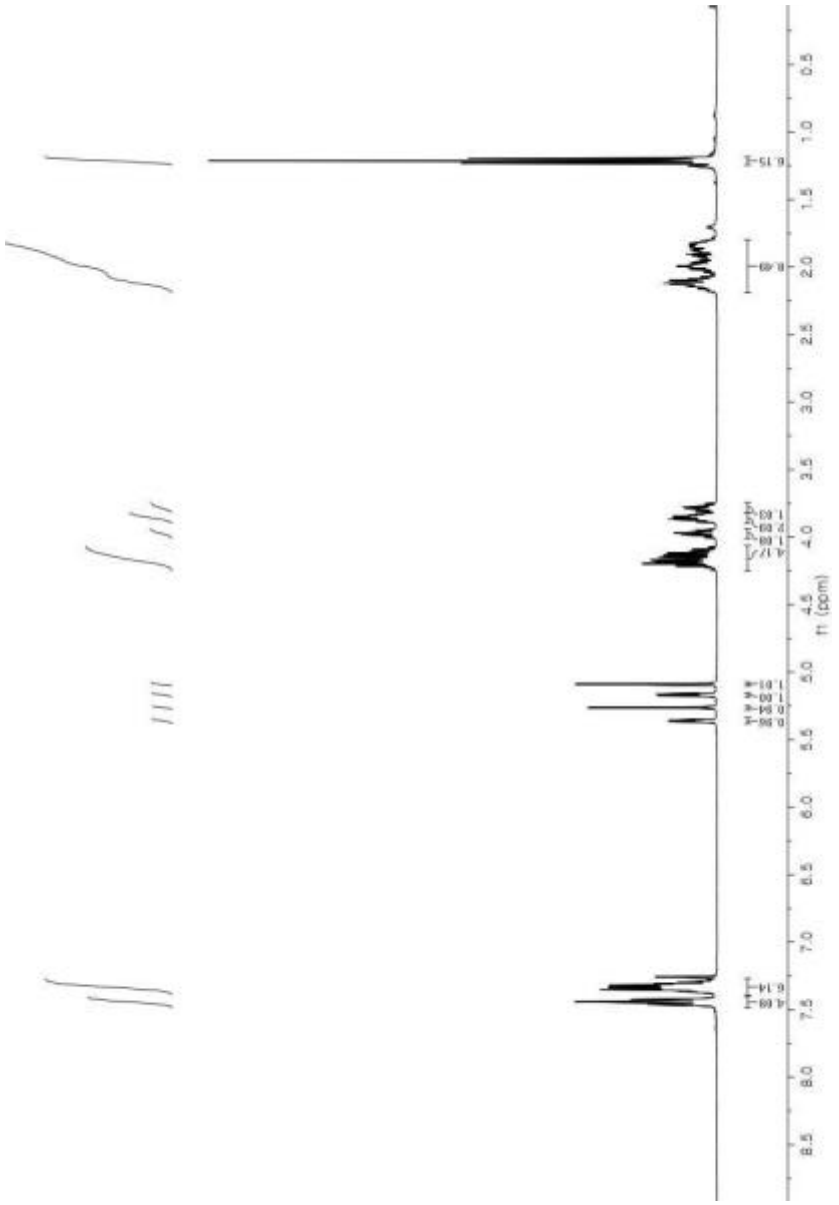
In accordance with Procedure B, **3.1a** (0.2 mmol, 100 mol%) was reacted with **3.2e** (13 x 100 mm pressure tube, 0.05 mL, 0.6 mmol, 300 mol%) in toluene (2.0 M) at 140 °C for a 24 hour period. Flash column chromatography (SiO_2: 2-5% ethyl acetate/hexanes) provided the title compound (39.0 mg, 0.23 mmol, *d.r.* = 1:1) as a pale yellow oil in 78% yield. NOTE: XPhos and $AdCO_2H$ was omitted.

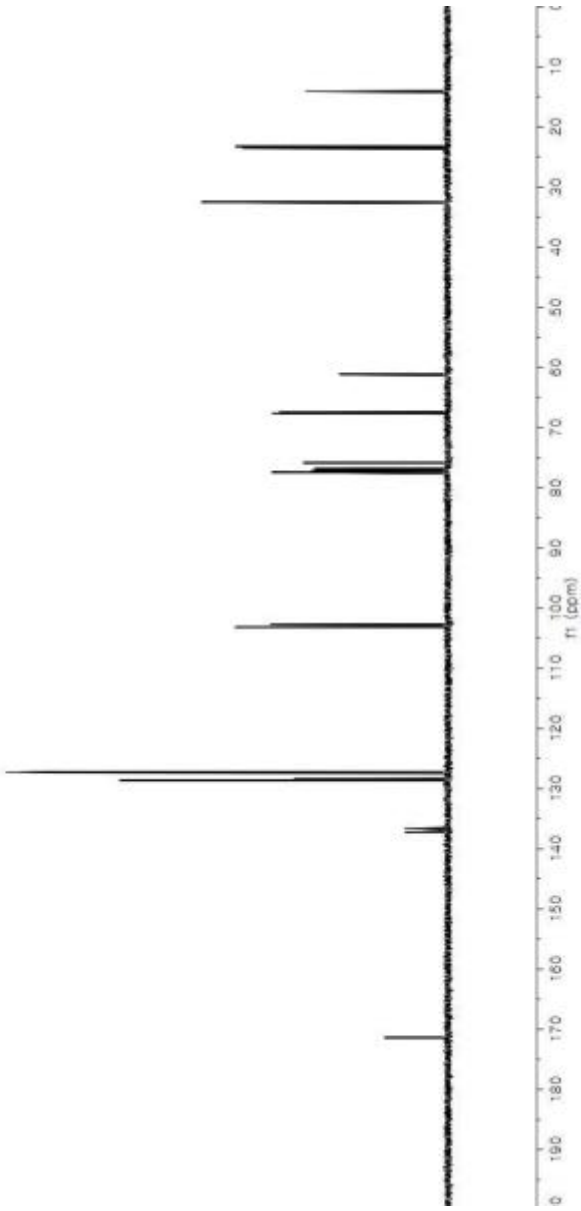
^{1}H NMR (400 MHz, $CDCl_3$): δ (A) 7.44 (ddd, *J* = 7.8, 7.8, 1.3 Hz, 2H), 7.39–7.27 (m, 3H), 5.36 (d, *J* = 3.6 Hz, 1H), 5.26 (s, 1H), 4.25–4.06 (m, 2H), 4.01–3.94 (m, 1H), 3.89–3.83 (m, 1H), 2.19–1.80 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 3H). (B) 7.44 (ddd, *J* = 7.8, 7.8, 1.3 Hz, 2H), 7.39–7.27 (m, 3H), 5.17 (d, *J* = 4.4 Hz, 1H), 5.09 (s, 1H), 4.25–4.06 (m, 2H), 3.89–3.83 (m, 1H), 3.81–3.77 (m, 1H), 2.19–1.80 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (A) 171.4, 137.2, 128.5, 128.4, 127.2, 102.7, 75.8, 67.5, 61.3, 32.6, 23.3, 14.2. (B) 171.4, 136.6, 128.64, 128.56, 127.4, 103.2, 77.4, 67.7, 61.1, 32.5, 23.6, 14.2.

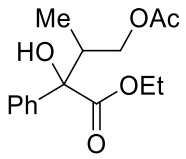
LRMS (ESI) Calcd. for $C_{14}H_{18}O_4$, $[M+Na]^+$: 273, Found: 273.

FTIR (neat): 2981, 1747.




f1 (ppm)

Ethyl 4-acetoxy-2-hydroxy-3-methyl-2-phenylbutanoate (3.3y).



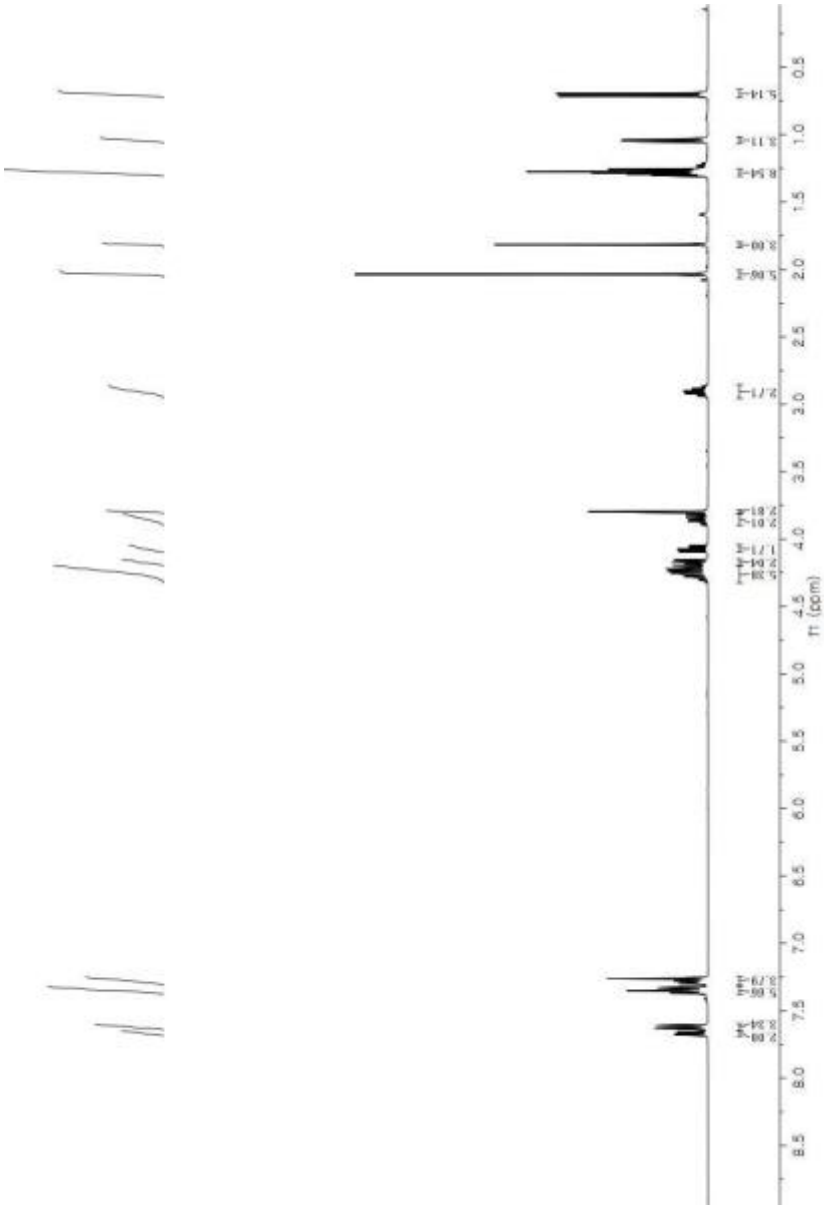
In accordance with Procedure B, **3.1a** (0.2 mmol, 100 mol%) was reacted with **3.2f** (13 x 100 mm pressure tube, 0.11 mL, 1.0 mmol, 500 mol%) in toluene (2.0 M) at 140 °C for a 40 hour period. Flash column chromatography (SiO_2: 5-7% ethyl acetate/hexanes) provided the title compound (33.6 mg, 0.12 mmol, *d.r.* = 1.6:1) as a pale yellow oil in 60% yield.

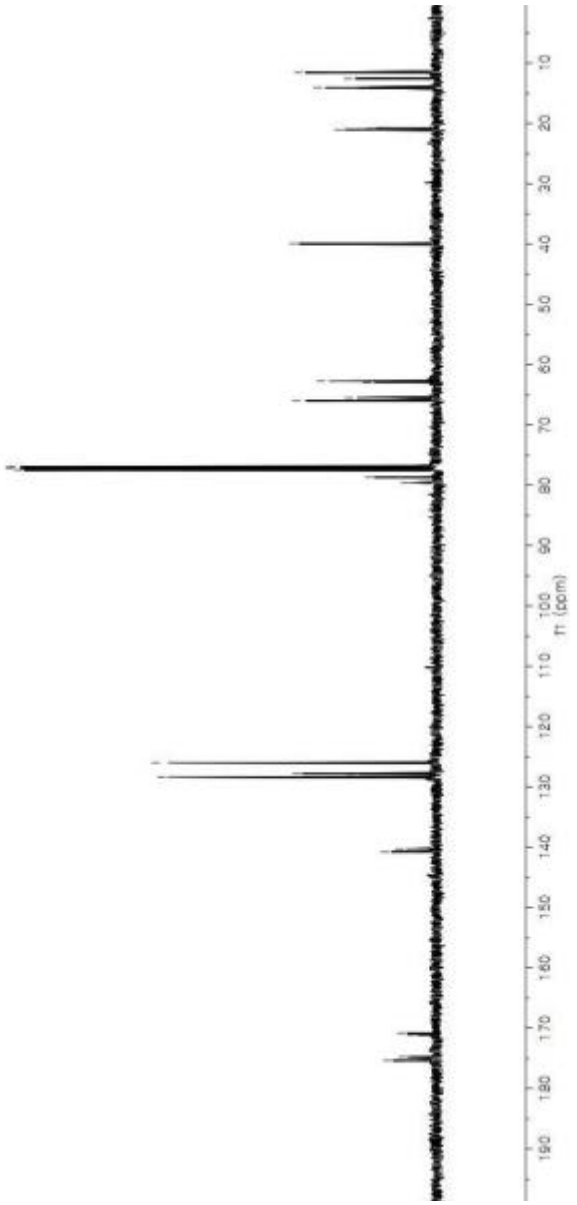
^{1}H NMR (400 MHz, $CDCl_3$): δ (major) 7.62 (ddd, *J* = 3.4, 1.9, 1.9 Hz, 2H), 7.35 (ddd, *J* = 11.8, 4.6 Hz, 3H), 4.33–4.15 (m, 3H), 4.07 (dd, *J* = 11.0, 6.5 Hz, 1H), 3.80 (s, 1H), 2.96–2.86 (m, 1H), 2.04 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H). (minor) 7.66 (ddd, *J* = 3.4, 1.9, 1.9 Hz, 2H), 7.31–7.25 (m, 3H), 4.33–4.20 (m, 2H), 3.90–3.81 (m, 2H), 3.80 (s, 1H), 2.96–2.86 (m, 1H), 1.81 (s, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (major) 175.3, 170.8, 140.8, 128.3, 127.8, 126.0, 78.7, 66.0, 62.7, 40.0, 21.0, 14.1, 11.6. (minor) 174.7, 171.1, 140.2, 128.4, 127.9, 125.9, 79.6, 65.5, 62.9, 40.1, 20.8, 14.2, 12.6.

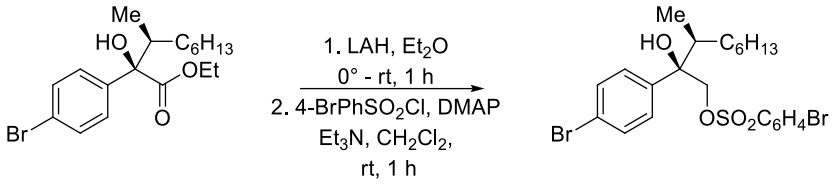
LRMS (ESI) Calcd. for $C_{15}H_{20}O_5$, $[M+Na]^+$: 303, Found: 303.

FTIR (neat): 3494, 2981, 1727, 1231.




f1 (ppm)

2-(4-bromophenyl)-2-hydroxy-3-methylnonyl 4-bromobenzenesulfonate (3.3q Derivative).



An ethereal solution (5 mL) of **3.3q** (1.39 g, 3.7 mmol) was added dropwise to a 100 mL round-bottom flask charged with an ethereal (30 mL, 0.12 M) suspension of LAH (709 mg, 18.7 mmol) at 0°C. The reaction was removed from the ice-bath and was allowed to stir (1 hr). Distilled water (1 mL) was added slowly. Distilled water (3 ml) and 15% NaOH aqueous (1 mL) were added to the reaction mixture. To the vigorously stirred solution was added portions of $MgSO_4$ until the reaction mixture solidified. The reaction mixture was filtered through a fritted glass funnel with the aid of ether. The filtrate was evaporated under reduced pressure and was used in the next step without further purification. To the crude diol (1.16g, 3.5 mmol) was added dichloromethane (30 ml, 1.1 M), 4-bromobenzenesulfonyl chloride (996 mg, 3.9 mmol), DMAP (42 mg, 0.35 mmol) and Et_3N (1 mL, 7.1 mmol). The reaction was allowed to stir at ambient temperature for one hour. $NaHCO_3$ (10 mL) and distilled water (10 ml) were added to the reaction mixture. The mixture was transferred to a separatory funnel and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine (1 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude 4b derivative residue was subjected to column chromatography (SiO_2: 20% ethyl acetate/hexanes) to give the title compound (1.7g, 3.3 mmol) in 90% yield as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.39. (d, *J* = 8.6, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 4.34 (s, 2H), 2.11 (s, 1H), 1.86 – 1.76 (m, 1H), 1.55 – 1.46 (m, 1H), 1.37 – 1.05 (m, 8H), 0.91 – 0.80 (m, 4H), 0.74 (d, *J* = 6.9 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 134.4, 132.6, 131.1, 129.2, 127.6, 74.7, 40.5, 31.8, 30.2, 29.4, 27.6, 22.6, 14.0, 13.8.

LRMS (ESI-MS) Calcd. for $C_{22}H_{28}Br_2O_4$ $[M+Na]^+$: 571, Found: 571.

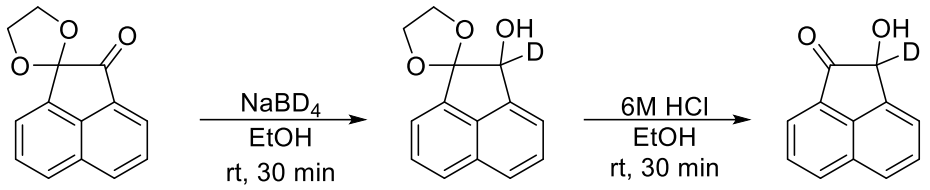
FTIR (neat): 3610, 2927, 1727, 1577.

MP: 98-100 °C.

2.98
4.28
8.33
0.98
0.99
0.99
1.96
2.06
2.01
1.96
2.00
ppm

20
40
60
80
100
120
140
160
180
ppm

2-hydroxyacenaphtylen-1(2H)-one-2-d (*deuterio*-3.1k).



To a flame-dried 50 mL round-bottom flask charged with 2*H*-spiro[acenaphthylene-1,2'-[1,3]dioxolan]-2-one (891 mg, 3.9 mmol) was added ethanol (20 ml, 0.2 M). $NaBD_4$ (180 mg, 4.3 mmol) was added portionwise. The reaction mixture was allowed to stir at ambient temperature for 30 min. Distilled water was added and the reaction mixture was allowed to stir until bubbling stopped. The mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (1 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Without further purification the crude alcohol residue was added ethanol (20 mL) and 6.0 M HCl aqueous (15 ml). The reaction mixture was allowed to stir at ambient temperature for the stated time. Distilled water was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (1 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The crude solid was subjected to column chromatography (SiO_2: 15% ethyl acetate in hexanes) to give the title compound (0.69g, 3.7 mmol) in 95% yield as a white solid.

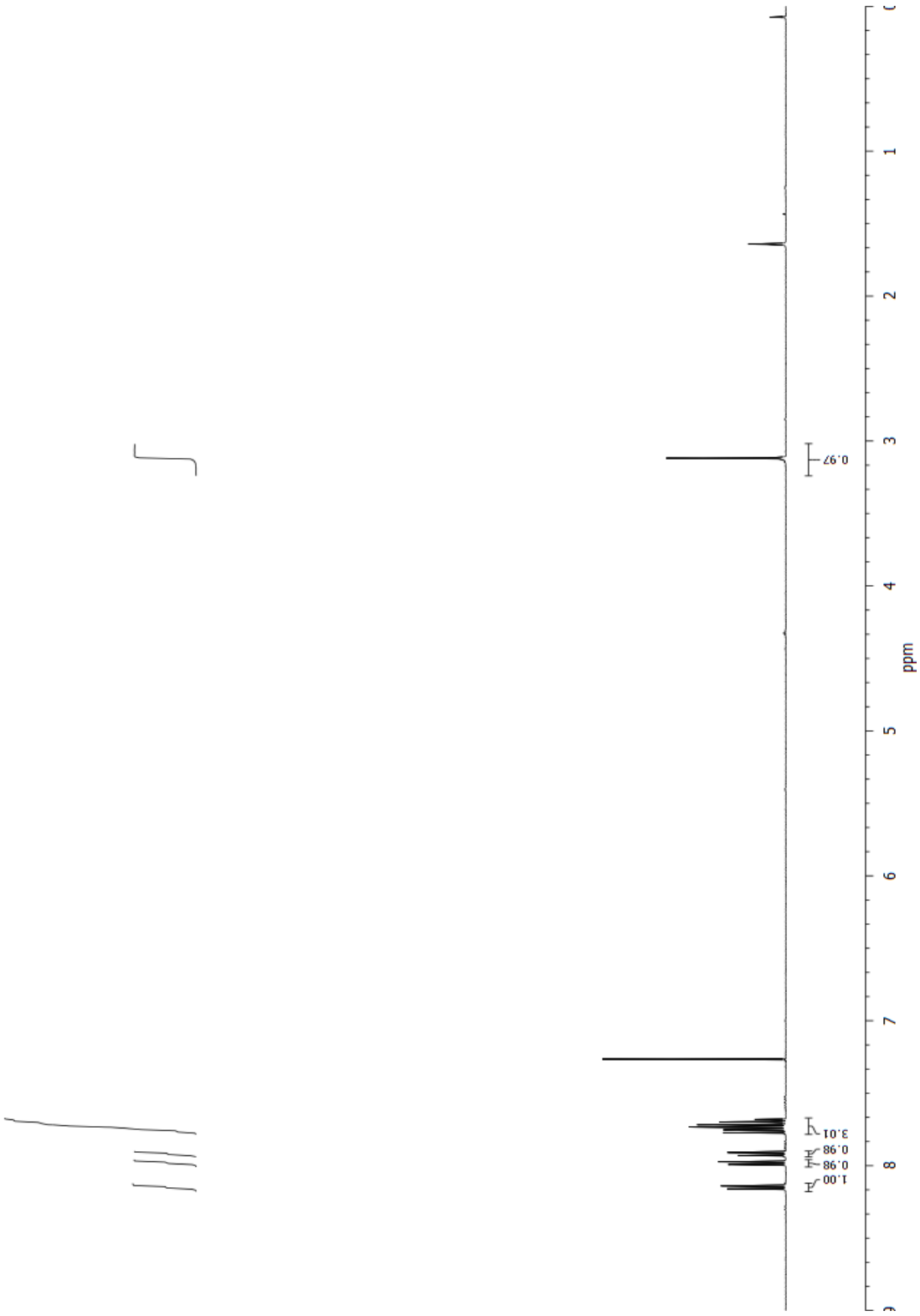
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 7.1 Hz, 1H), 7.92. (dd, *J* = 8.1, 1.1 Hz, 1H), 7.79 – 7.66 (m, 3H), 3.12 (s, 1H).

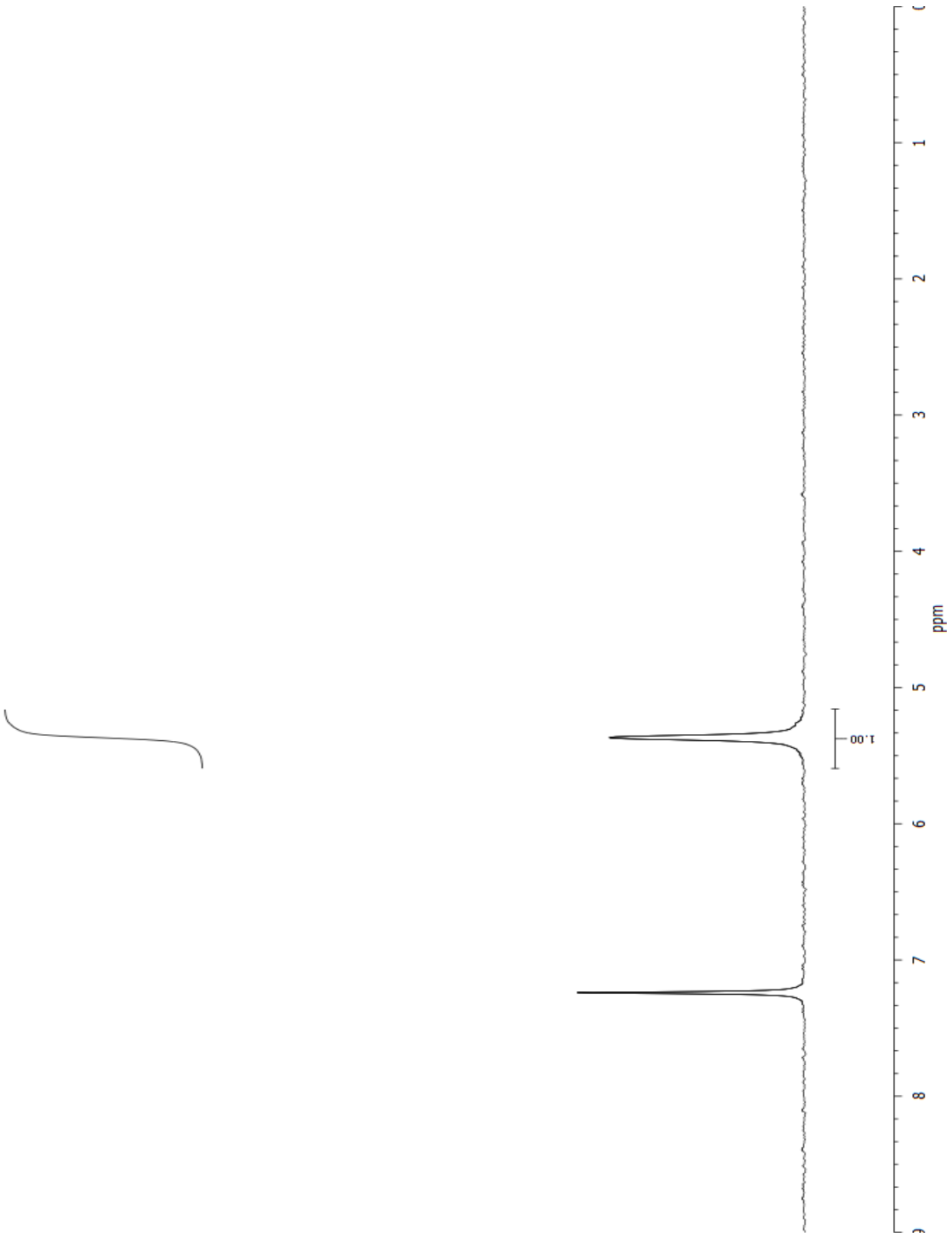
^{2}H NMR (77 MHz, $CHCl_3$): δ 5.37 (s, 1D).

HRMS (ESI-MS) Calcd. for $C_{12}H_7DO_2$ $[M+Na]^+$: 208.0479, Found: 208.0460.

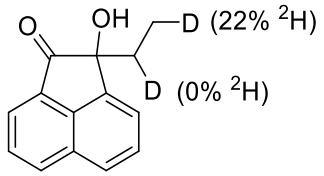
FTIR (neat): 3400, 3064, 1702.

MP: 160-162 ^oC.


0.97
3.01
0.98
0.98
1.00
ppm


1.00
ppm

2-(ethyl-1,2-d2)-2-hydroxyacenaphthylen-1(2H)-one (*deuterio*-3.3k).



In accordance with Procedure A, *deuterio*-**3.1k** (0.2 mmol, 100 mol%) was reacted with ethylene (15 x 125 mm pressure tube, 0.82 mmol, 410 mol%) in toluene (2.0 M) at 130 °C for a 48 hour period. Flash column chromatography (SiO_2: 5-15% ethyl acetate/hexanes) provided the title compound (18.0 mg, 0.08 mmol) in 42% yield as a white solid.

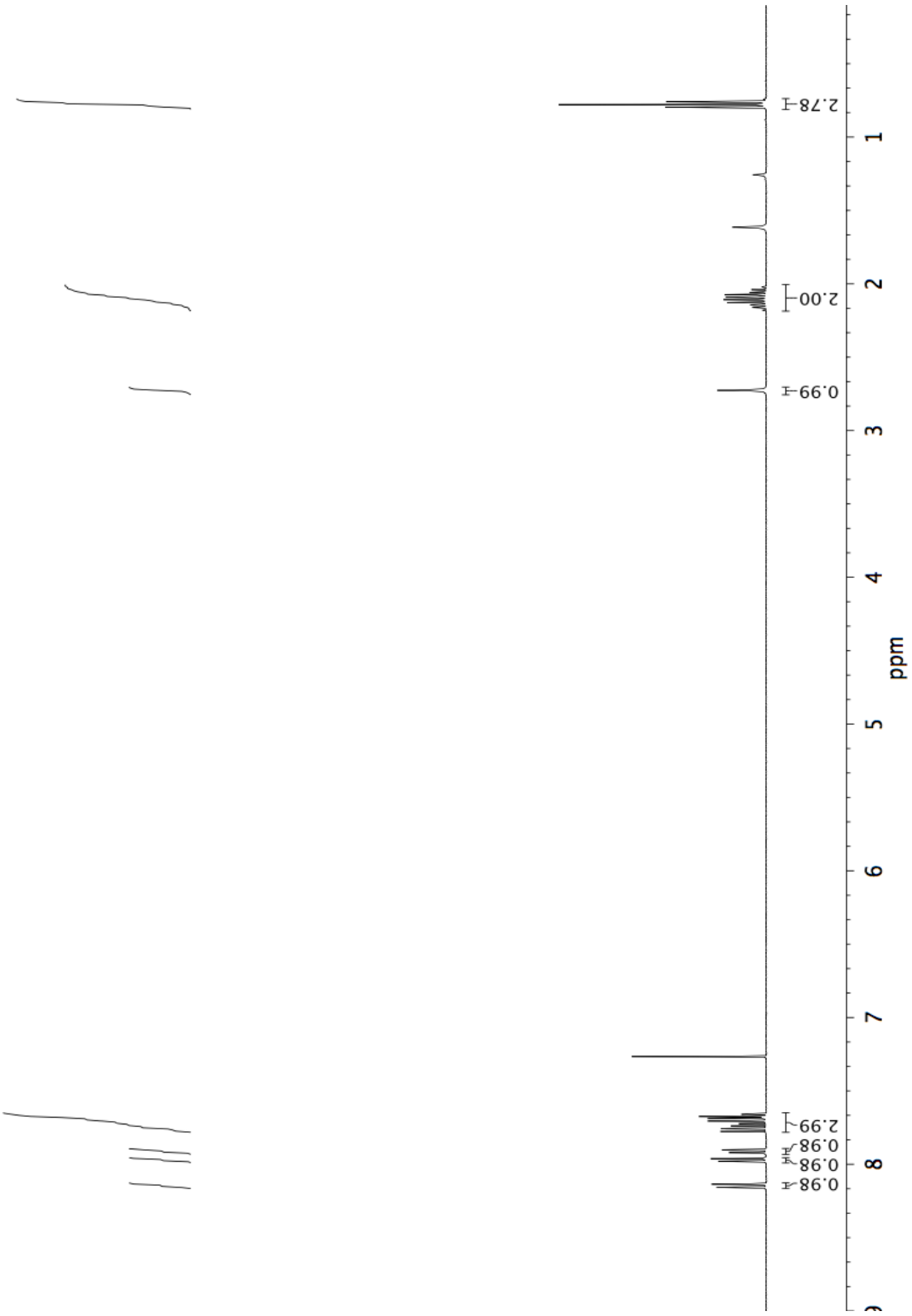
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 7.0 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.79 – 7.64 (m, 3H), 2.72 (s, 1H), 2.19–2.01 (m, 2H), 0.78 (t, *J* = 7.5 Hz, 2.78H).

^{2}H NMR (77 MHz, $CHCl_3$): δ 0.77 (s, 0.22H).

HRMS (ESI-MS) Calcd. for $C_{14}H_{11}DO_2$ $[M+Na]^+$: 236.0792, Found: 236.0781.

FTIR (neat): 3370, 2973, 2927, 1716.

MP: 92-93 °C.


2.78
2.00
0.99
2.99
0.98
0.98
0.98
ppm
1
2
3
4
5
6
7
8

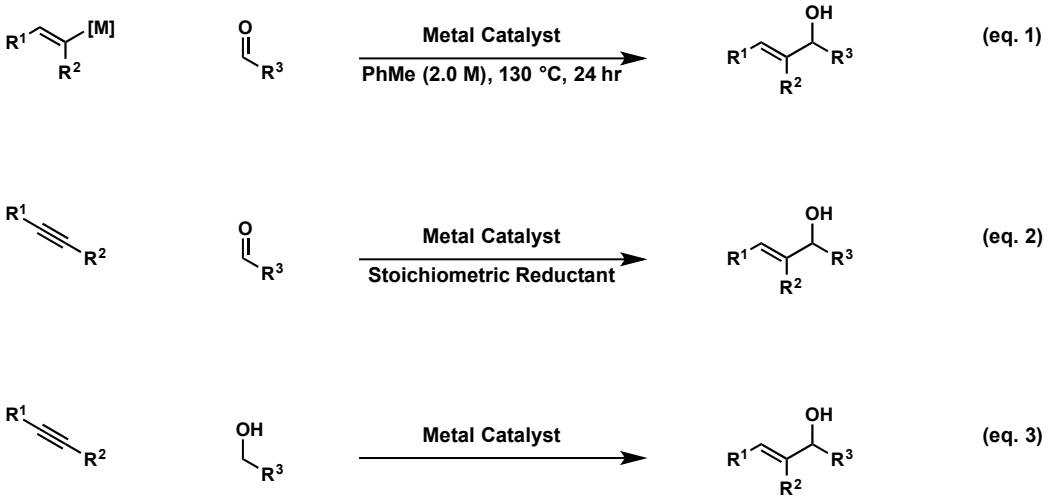
8
7
6
5
4
3
2
1
ppm

Chapter 4: Vinyl Transfer from Enol Carboxylates via Transition Metal Catalysis by way of Metallacycle Fragmentation

4.1 Introduction

The synthesis of allylic alcohols can be conducted by carbonyl addition with the use of stoichiometric use of vinylmetal reagents (**Scheme 4.1**, eq. 1).[65,66] Other methods in obtaining allylic alcohols take advantage of metal-catalyzed reactions through an alkyne-carbonyl reductive coupling approach.[38,67–69] However, a limitation of this approach uses stoichiometric reductants, with the exception of hydrogen-mediated processes **(Scheme 4.1**, eq. 2).[67,68] More recently the studies of redox-neutral alcohol-alkyne vinylations have been developed using ruthenium and nickel catalysts (**Scheme 4.1**, eq. 3).[33,51,70]

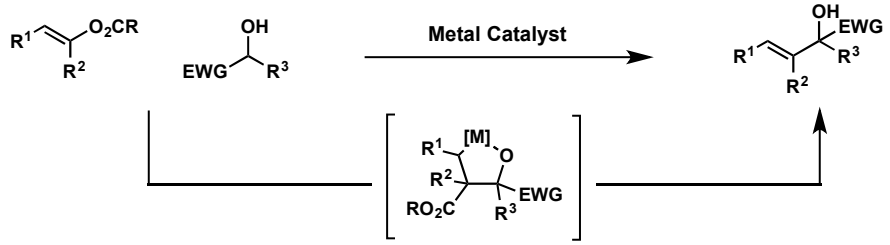
Scheme 4.1: Metal catalyzed vinyl transfer processes



A new strategy has been developed in the Krische group where in a catalytic process using transition metals, products of vinyl transfer can be obtained through an E1cB-like fragmentation of metallacycles (**Scheme 4.2**).[71] Stoichiometric reactions have

been reported using early transition metals.[31,72–74] This new catalytic method enables the direct vinylations of secondary alcohol C-H bonds in vicinally dioxygenated systems.

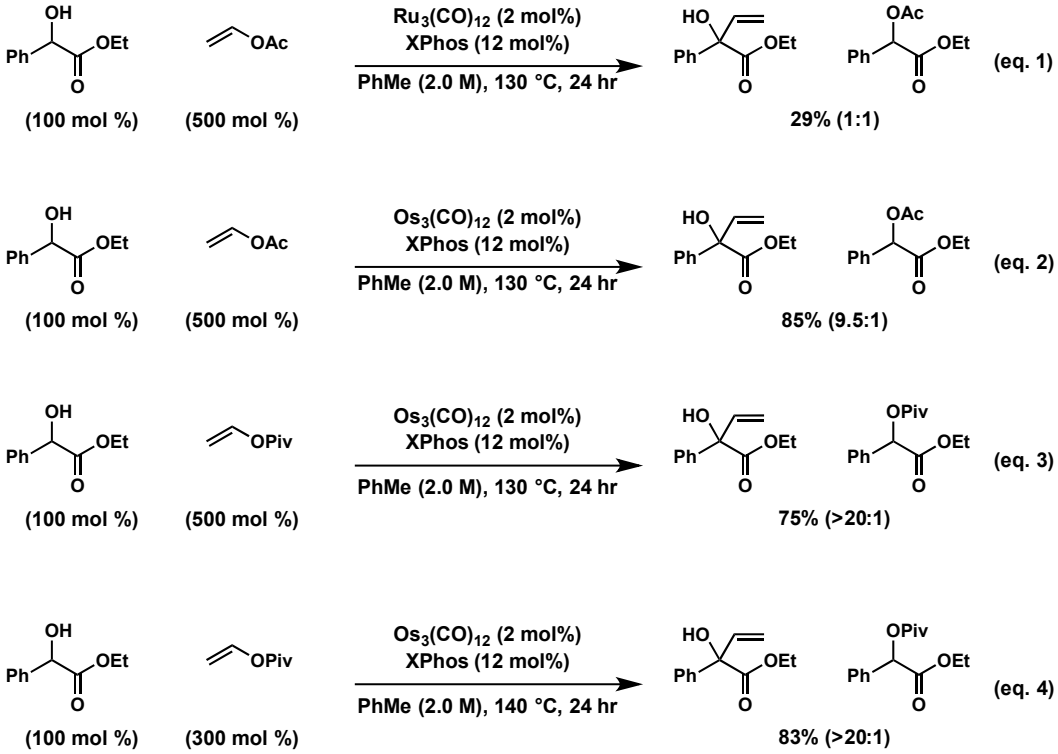
Scheme 4.2: Catalytic metal catalyzed vinyl transfer *via* metallacycle fragmentation



4.2 Reaction Development and Scope

Initial experiments involving ethyl mandelate with vinyl acetate were inspired by previously established conditions for ruthenium (0) coupling reactions developed in the Krische group[51] and other studies by Chatani and Murai[6] on their work on ruthenium (0) Pauson-Khand reactions. Initial conditions only delivered traced amount of products, which prompted further optimization (**Scheme 4.3**).

Scheme 4.3: Selected optimization experiments for vinyl transfer using ethyl mandelate



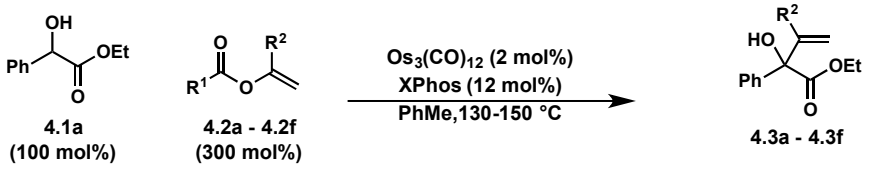
With the use of a ruthenium metal modified by XPhos, a Buchwald type ligand, delivered the desired vinylation product in 29% yield as a 1:1 mixture with the acyl substitution byproduct (**Scheme 4.3**, eq. 1). The switch to a more reducing metal such as $Os_3(CO)_{12}$ lead to a higher yield of the desired vinylation product along with the acyl substituted product once again, but now in a 9.5:1 ratio (**Scheme 4.3**, eq. 2). The enhanced performance of the osmium catalyst can be understood on the basis of π-backbonding.[53,75] The increased reactivity of the osmium catalyst was chosen as the catalyst of choice and the focus was to now minimize the amount of acyl substituted product. The use of a bulkier enol carboxylate such as vinyl pivalate from vinyl acetate was implemented and delivered the desired product exclusively (**Scheme 4.3**, eq. 3). The bulkier enol carboxylate increased selectivity but delivered a slight decrease in yield of

the desired product. Further optimization leading to the deemed optimal condition provided the desired product in 83% yield with the increase in temperature and lower loadings of the enol carboxylate. (**Scheme 4.3**, eq. 4).

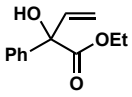
To assess the generality of the reaction, the optimal conditions were applied to a variety of enol carboxylate derivatives to ethyl mandelate (**Table 4.1**). It was found that the use of more highly substituted enol carboxylates was not as efficient with vinyl pivalates leading to *O*-acylation products. The use of corresponding triphenyl acetates suppresses the *O*-acylation products and delivers the desired vinylation products in moderate to good yields. 1,1-Disubstituted alkenes could be obtained by this was giving products bearing alkyl, cycloakyl and aryl groups **4.3b-f**. Another activated secondary alcohol such as *N*-benzyl-3-hydroxy-2-oxindole was also subjected to a parallel set of vinyl transfer experiments (**Table 4.2**). One noteworthy observation to is that the reaction involving *N*-benzyl-3-hydroxy-2-oxindoles with enol carboxylates were performed under $Ru_3(CO)_{12}$ rather than its osmium counterpart. The rationale for being able to use a less reducing metal could reside from the dehydrogenation of the *N*-benzyl-3-hydroxy-2-oxindole gives rise to the highly reactive isatin the readily engages in oxidative coupling with the present enol carboxylate. The reactivity of *N*-benzyl-3-hydroxy-2-oxindoles also attenuates the *O*-acylation for most cases, with the exception of **4.3k** and **4.3l** which then required vinyl pivalate over vinyl acetate. In the most extreme case for the *N*-benzyl-3-hydroxy-2-oxindoles the triphenyl acetate had to be employed for the formation of the alkene bearing a cyclopropyl ring **4.3i**, due to the competing *O*-acylation once again. It was also shown that transfer of trisubstituted alkenes could also be added to *N*-benzyl-3-hydroxy-2-oxindoles in the form of conjugated enones (**Scheme 4.4**). Finally, vinyl

transfer can also be performed from the carbonyl oxidation state, by using isopropanol as a terminal reductant (**Scheme 4.5**).

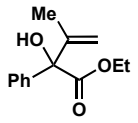
Table 4.1: Osmium-catalyzed vinyl transfer to α-ketoester



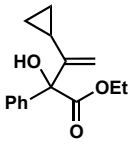
$R^1 = {}^t$Bu, R^2 = H, 4.2.a	$R^1 = CPh_3$, R^2 = Me, 4.2.b	$R^1 = CPh_3$, R^2 = *c*-propyl, 4.2.c
$R^1 = {}^t$Bu, R^2 = Ph, 4.2.d	$R^1 = {}^t$Bu, R^2 = 3,5-$(CF_3)_2$Ph, 4.2.e	$R^1 = CPh_3$, R^2 = benzodioxle, 4.2.f



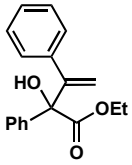
4.3a, 83% Yield



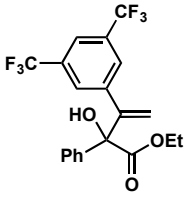
4.3b, 80% Yield



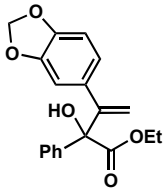
4.3c, 65% Yield



4.3d, 71% Yield

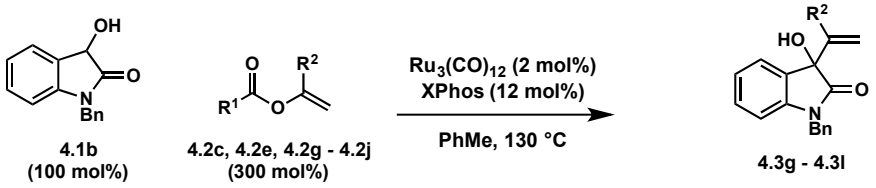


4.3e, 80% Yield

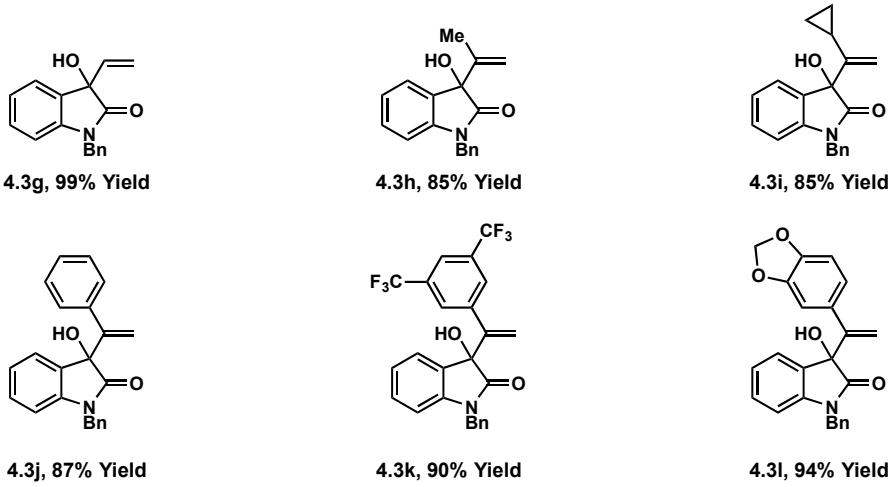


4.3f, 68% Yield

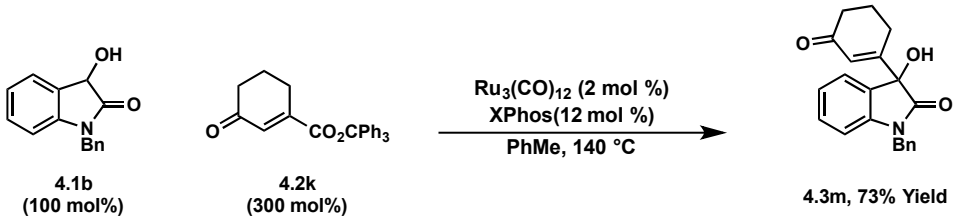
Table 4.2: Ruthenium-catalyzed vinyl transfer to *N*-benzyl-3-hydroxy-2-oxindoles



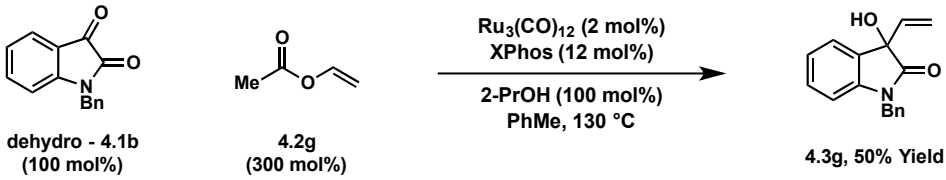
R^1 = Me, R^2 = H, 4.2.g	R^1 = Me, R^2 = Me, 4.2.h	R^1 = CPh_3, R^2 = *c*-propyl, 4.2.c
R^1 = Me, R^2 = Ph, 4.2.i	R^1 = ^{t}Bu, R^2 = 3,5-$(CF_3)_2$Ph, 4.2.e	R^1 = ^{t}Bu, R^2 = benzodioxle, 4.2.j



Scheme 4.4: Conjugate enones as vinyl transfer reagents to *N*-benzyl-3-hydroxy-2-oxindoles

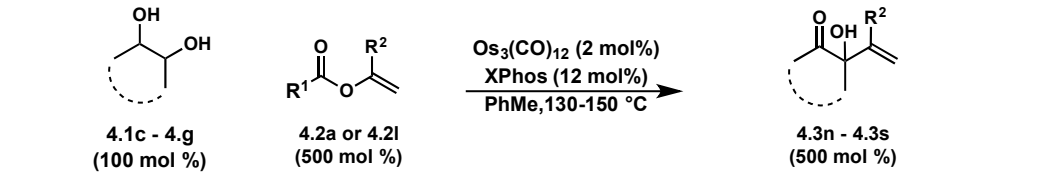


Scheme 4.5: Ruthenium-catalyzed vinyl transfer to *N*-benzyl-isatin

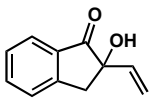


Vicinal diols were also explored as coupling partners to enol carboxylates such as vinyl pivalate and the triphenyl acetate (**Table 4.3**). The reactions involving vicinal diols are oxidative and require further excess of the vinyl partner as sacrificial hydrogen acceptor. Aryl and alkyl substituted diols formed products of vinylation in moderate to good yields. For the case of unsymmetrical diols **4.1c**, **4.1d**, **4.2f**, and **4.2g** the vinyl transfer adds exclusively to the carbonyl distal to the aryl ring.

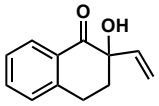
Table 4.3: Osmium-catalyzed vinyl transfer to 1,2-diols



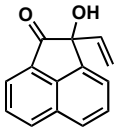
trans-indane-1,2-diol, 4.1c	*trans*-tetrahydronapthalene-1,2-diol, 4.1d	*trans*-dihydroacenapthalene-1,2-diol, 4.1e
cis-chroman-3,4-diol, 4.2f	*cis*-2,2-dimethylchroman-3,4-diol, 4.2g	*trans*-cyclohexane-1,2-diol, 4.2.h



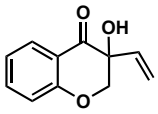
4.3n, 67% Yield
(R^1=^{t}Bu, R^2 = H, 4.2.a)



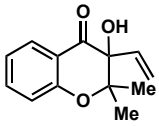
4.3o, 70% Yield
(R^1=^{t}Bu, R^2 = H, 4.2.a)



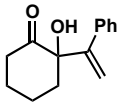
4.3p, 60% Yield
(R^1=^{t}Bu, R^2 = H, 4.2.a)



4.3q, 88% Yield
(R^1=^{t}Bu, R^2 = H, 4.2.a)



4.3r, 87% Yield
(R^1=^{t}Bu, R^2 = H, 4.2.a)



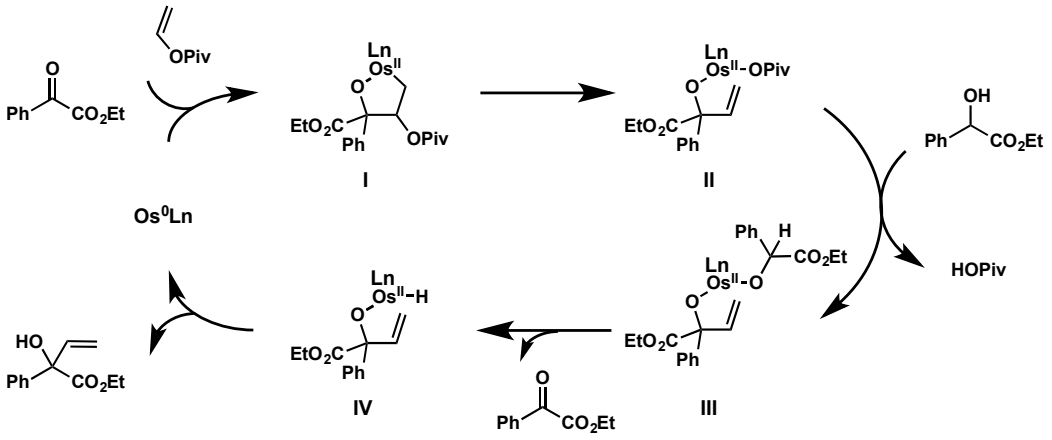
4.3s, 40% Yield
(R^1 = CPh_3, R^2 = Ph, 4.2.l)

4.3 PROPOSED MECHANISM

A plausible catalytic mechanism (**Figure 4.1**) starts with the dehydrogenation of ethyl mandelate to provide the ketoester which can then undergo oxidative coupling with the enol carboxylate and osmium (0) catalyst to form the oxaosmacycle **I**. Upon metallacycle fragmentation of oxaosmacycle **I** provides the osmium alkoxide **II** which

can then undergo a proton exchange to furnish osmium alkoxide **III**. Osmium alkoxide **III** then undergoes a β-hydride elimination providing another molecule of the ketoester derived from ethyl mandelate to re-enter the catalytic cycle and osmium hydride **IV**. Lastly osmium hydride **IV** undergoes a C-H reductive elimination to furnish the vinyl product and regenerating the osmium (0) catalyst, thus closing the catalytic cycle.

Figure 4.1: Proposed catalytic mechanism for metal catalyzed metallacycle fragmentation



4.4 CONCLUSION

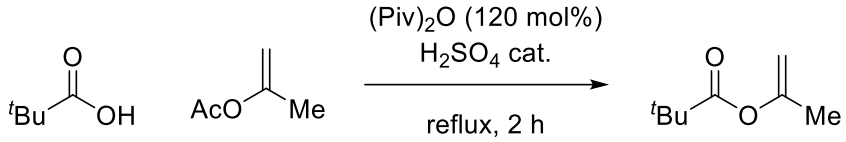
In summary, a new strategy to install vinyl moieties by way of metallacycle fragmentation has been shown. Reactivity of secondary alcohols can guide the use of either ruthenium (0) or osmium (0) catalyst to perform the mentioned transformation. Future studies will focus on the development of related catalytic systems to convert lower alcohols to higher alcohols in the absence of stoichiometric byproducts.

4.5 EXPERIMENTAL SECTION

General Information: All reactions were run under an atmosphere of argon. Pressure tubes (13x100 mm) were purchased from Fischer Scientific (catalog number 14–959–35C) and were flame dried followed by cooling in a desiccator. Toluene was dried over sodium metal, benzophenone, and distilled immediately prior to use. Anhydrous solvents were transferred by oven-dried syringes. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynanmic Absorbents F_{254}). Visualization was accomplished with UV light followed by dipping in Seebach's stain solution then heating. Purification of reactions was carried out by flash chromatography using Silacycle silica gel (40–63 μm). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+H, M+Na), or a suitable fragment ion. ^{1}H Nuclear magnetic resonance spectra were recorded using a 400 MHz spectrometer. Coupling constants are reported in Hertz (Hz) for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm). ^{13}C Nuclear magnetic resonance spectra were recorded using a 100 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to residual $CDCl_3$ δ_C (77.16 ppm).

Procedure for Synthesis of enol carboxylates:

Prop-1-en-2-yl pivalate (4.2h).



In modification to literature procedure,[76] a flame-dried 250 mL round-bottom flask was charged with pivalic acid (10 mL, 8.0 mmol), and pivalic anhydride (20 mL, 9.9 mmol). Then 50 mL of isopropenyl acetate was added followed by 2 drops of concentrated sulfuric acid. The stirred mixture was heated to reflux for 24 h. The mixture was allowed to cool to room temperature, and was then quenched with saturated sodium bicarbonate. The isopropenyl acetate was then removed by evaporation under reduced pressure. The residue was purified by vacuum distillation. When the distillated compound included impurities, it was further subjected to flash column chromatography (SiO_2, 2% Et_2O/pentanes) to furnish the title compound (560 mg, 8%) as a colorless oil.

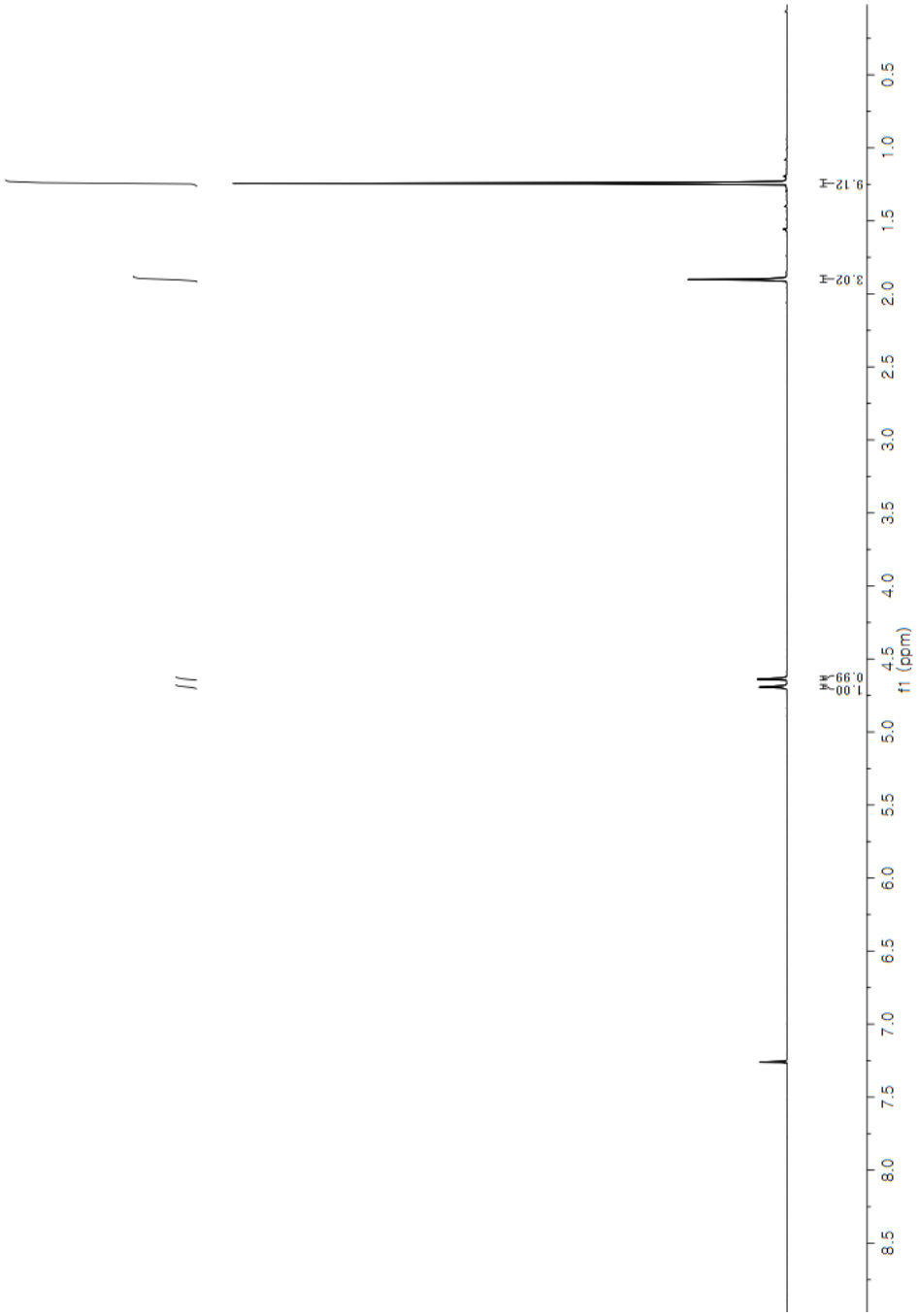
R_f : 0.48 (hexanes:DCM = 3:2).

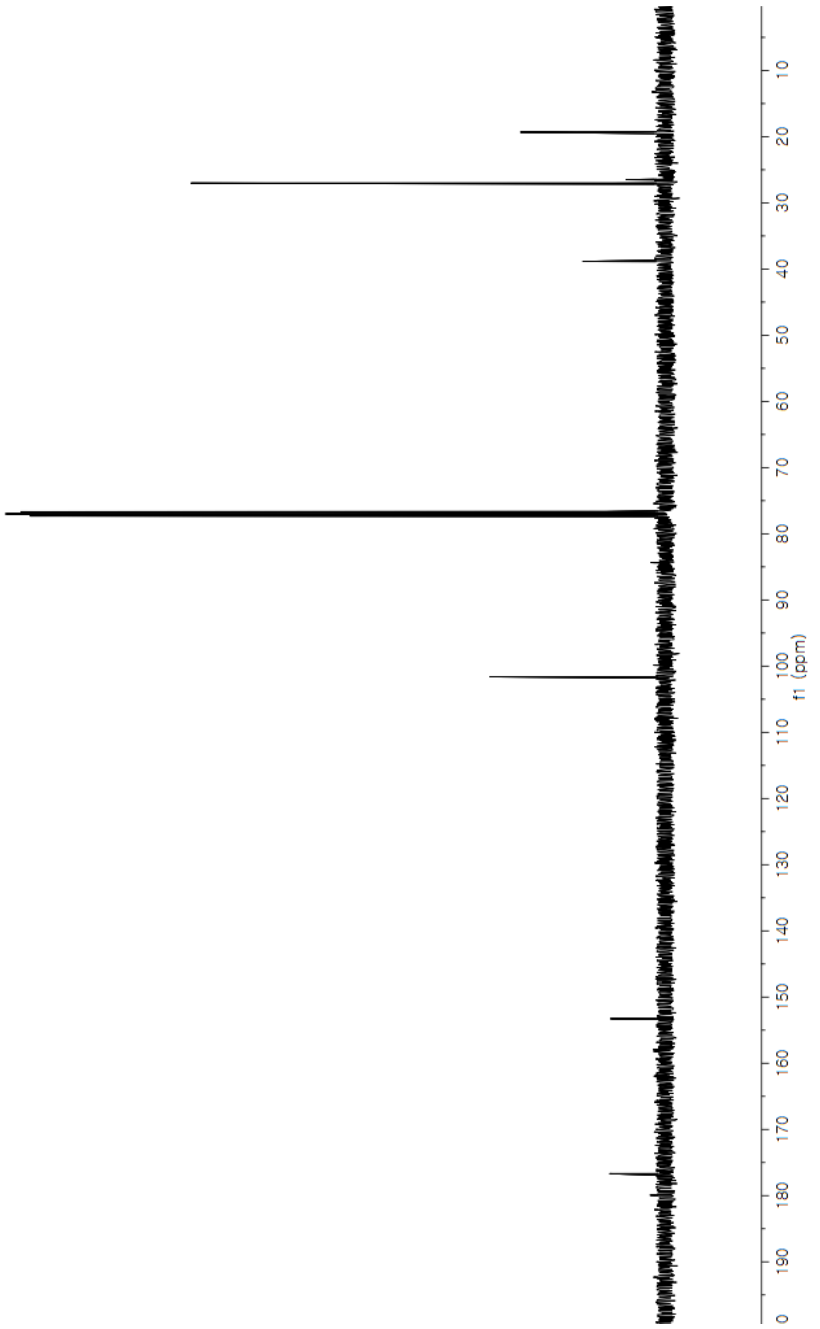
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.69 (s, 1H), 4.64 (s, 1H), 1.90 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 153.4, 101.8, 39.0, 27.2, 19.5.

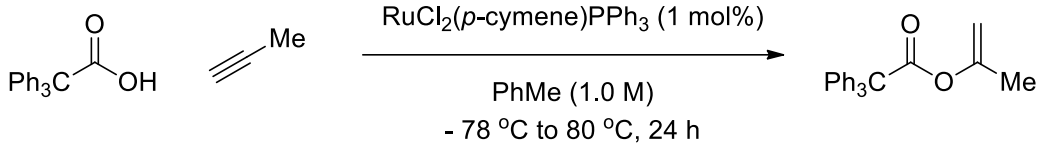
LRMS (CI) Calcd. for $C_8H_{14}O_2$ $[M+H]^+$: 143, Found: 143.

FTIR (neat): 2959, 2926, 1729.


9.12
3.02
1.00
0.99
f1 (ppm)


0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

Prop-1-en-2-yl 2,2,2-triphenylacetate (4.2b)



In modification to literature procedure,[77] to a 100 mL pressure tube were added α,α-diphenylbenzeneacetic acid (2.9 g, 10 mmol) and $RuCl_2$(*p*-cymene)PPh_3 (57 mg, 0.1 mmol) in 10 mL of toluene. Then, condensed methyl acetylene (3.7 mL, 50 mmol) was added to the solution at -78 ˚C. The reaction mixture was stirred at 80 ˚C for 24 h. The solution was diluted with Et_2O and quenched with water. The aqueous phase was extracted with Et_2O (2 x 20 mL), then the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was subjected to flash column chromatography (SiO_2, 20% DCM/hexanes to 30% DCM/hexanes) to furnish the title compound (1.4 g, 43%) as a white solid.

R_f: 0.45 (hexanes:DCM = 3:2).

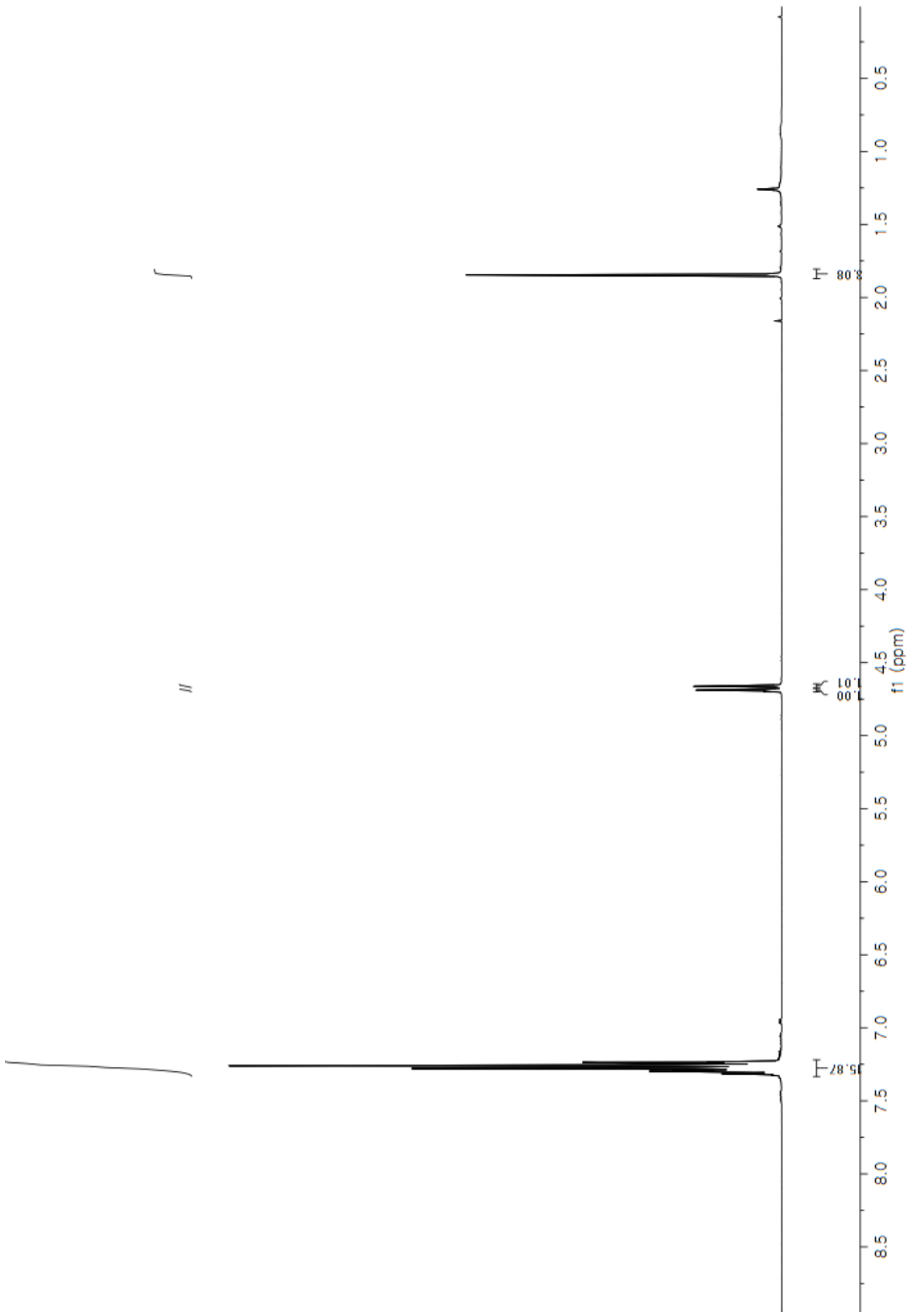
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.23 (m, 15H), 4.70–4.68 (m, 1H), 4.66 (d, *J* = 1.2 Hz, 1H), 1.85 (s, 3H).

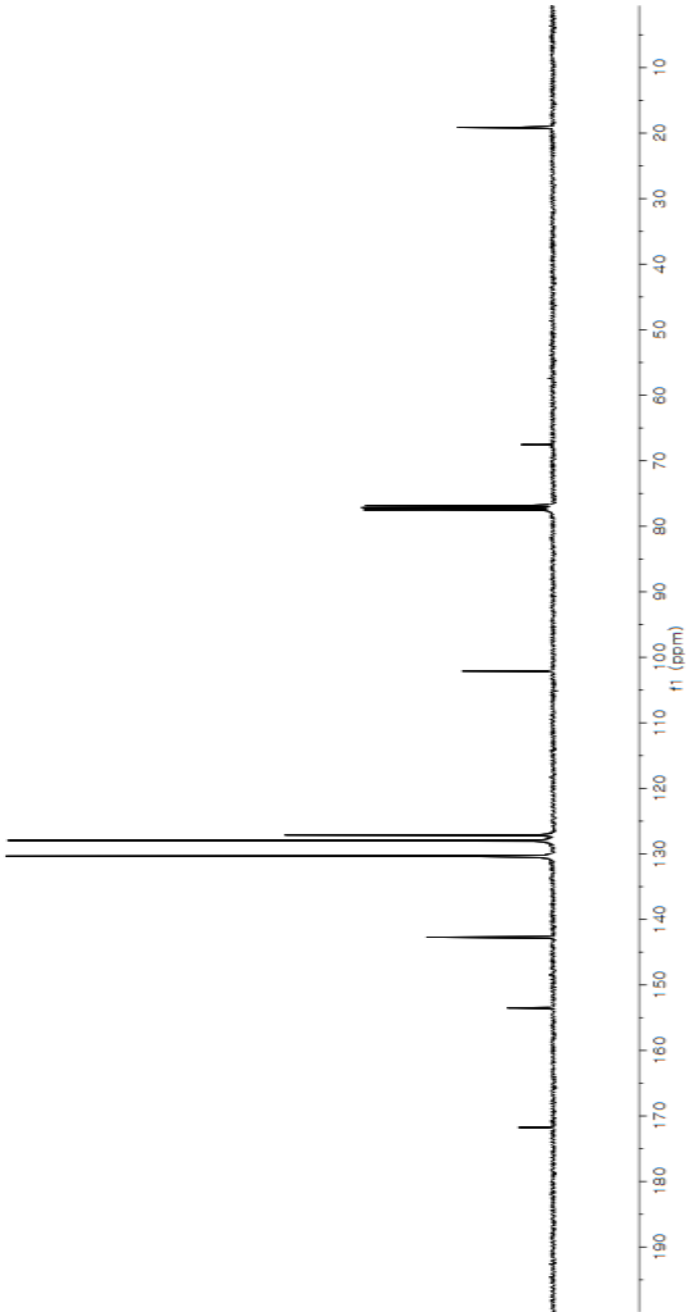
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 153.5, 142.7, 130.4, 127.9, 127.1, 102.1, 67.6, 19.1.

LRMS (CI) Calcd. for $C_{23}H_{20}O_2$ $[M+H]^+$ and $[CPh_3]^+$: 329 and 243, Found: 329 and 243.

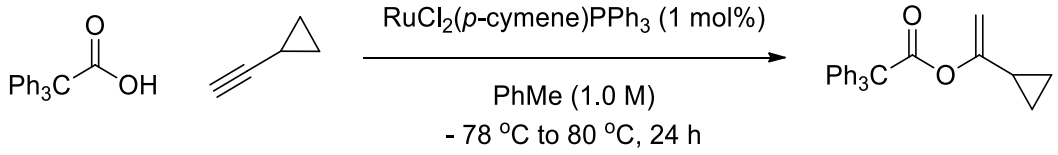
FTIR (neat): 2359, 1737.

MP: 100.2–102.4 °C.


15.87
8.08
1.01
1.00
f1 (ppm)


f1 (ppm)

1-Cyclopropylvinyl 2,2,2-triphenylacetate (4.2c)



In modification to literature procedure,[77] a flame-dried 100 mL round-bottom flask was charged with cyclopropyl acetylene (1.3 mL, 15 mmol), α,α-diphenylbenzeneacetic acid (2.9 g, 10 mmol), and $RuCl_2$(*p*-cymene)PPh_3 (57 mg, 0.1 mmol) in 10 mL of toluene. The reaction mixture was stirred at 80 ˚C for 24 h. The solution was diluted with Et_2O and quenched with water. The aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was subjected to flash column chromatography (SiO_2, 2% EtOAc/hexanes) to furnish the title compound (2.5 g, 70%) as a white solid.

R_f : 0.45 (hexanes:DCM = 3:2).

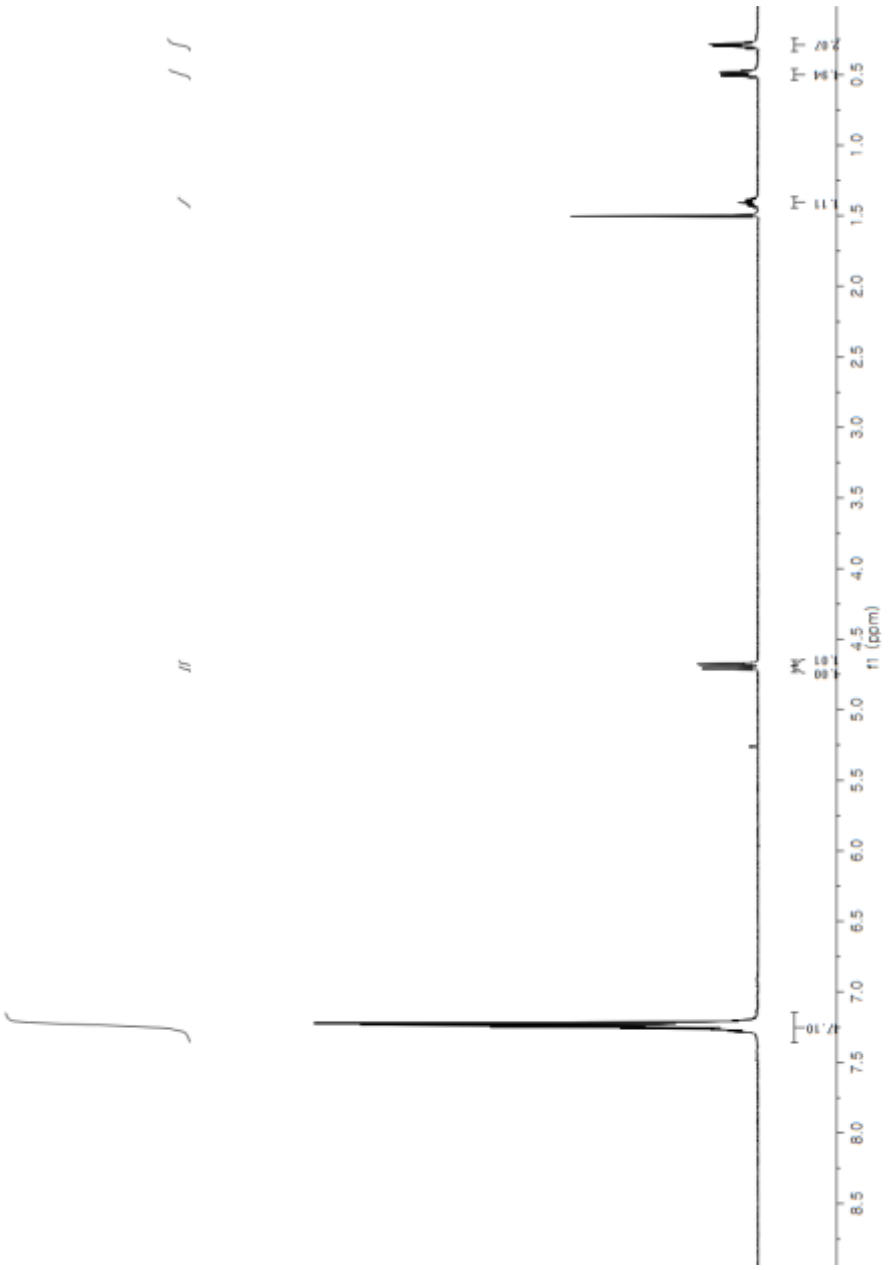
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.20 (m, 15H), 4.71 (d, *J* = 2.0 Hz, 1H), 4.68 (d, *J* = 2.0 Hz, 1H), 1.44–1.38 (m, 1H), 0.52–0.47 (m, 2H), 0.31–0.27 (m, 2H).

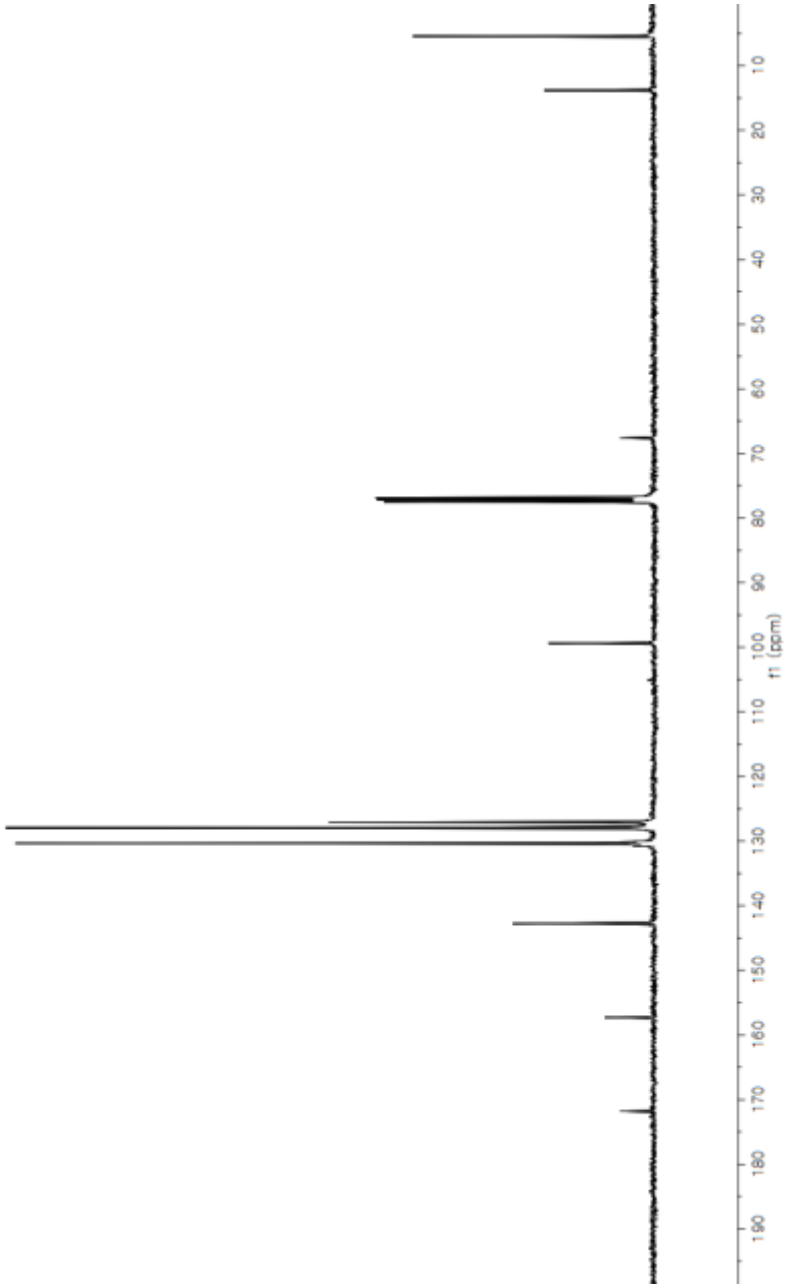
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 157.3, 142.7, 130.7, 130.3, 127.9, 127.1, 99.4, 67.6, 13.8, 5.4.

LRMS (CI) Calcd. for $C_{25}H_{22}O_2$ $[M+H]^+$ and $[CPh_3]^+$: 355 and 243, Found: 355 and 243.

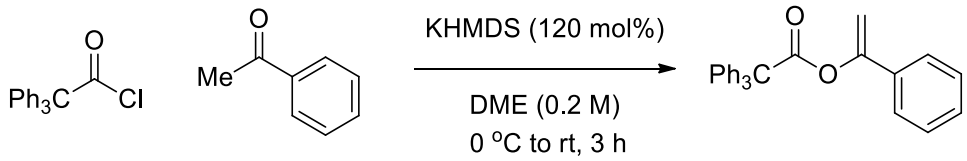
FTIR (neat): 2359, 1735, 1175.

MP: 92.8–95.6 ºC.


2.87
1.94
1.11
2.80
1.81
47.10
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

1-Phenylvinyl 2,2,2-triphenylacetate (4.2l)



A flame-dried 50 mL round-bottom flask was charged with potassium bis(trimethylsilyl)amide (KHMDS) (1.6 g, 7.9 mmol) and DME (8 mL). To this stirring mixture aceteophenone (0.77 mL, 6.6 mmol) was added dropwise. The resulting solution was stirred for an additional 15 min and was then transferred dropwise *via* syringe to another 50 mL round-bottom flask with triphenylacetyl chloride (3.0 g, 9.8 mmol) in DME (8 mL) at 0 °C. The reaction mixture was stirred for 3 hours, and then quenched with NH_4Cl (10 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were successively washed with water (3 × 10 mL) and brine (3 × 10 mL), and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexanes) to afford the title compound (1.9 g, 74%) as a pale white solid.

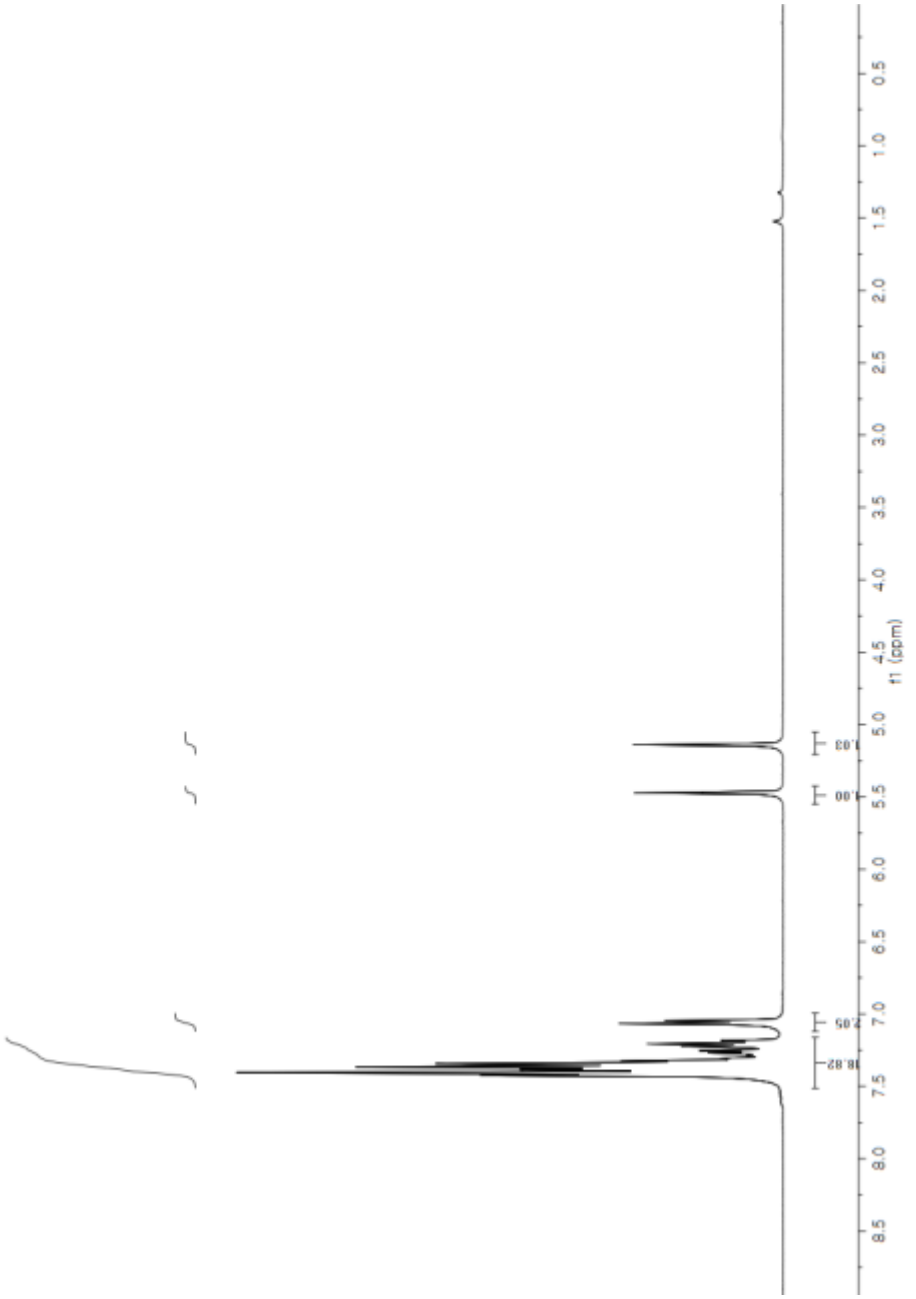
R_f : 0.60 (EtOAc:hexanes = 1:4).

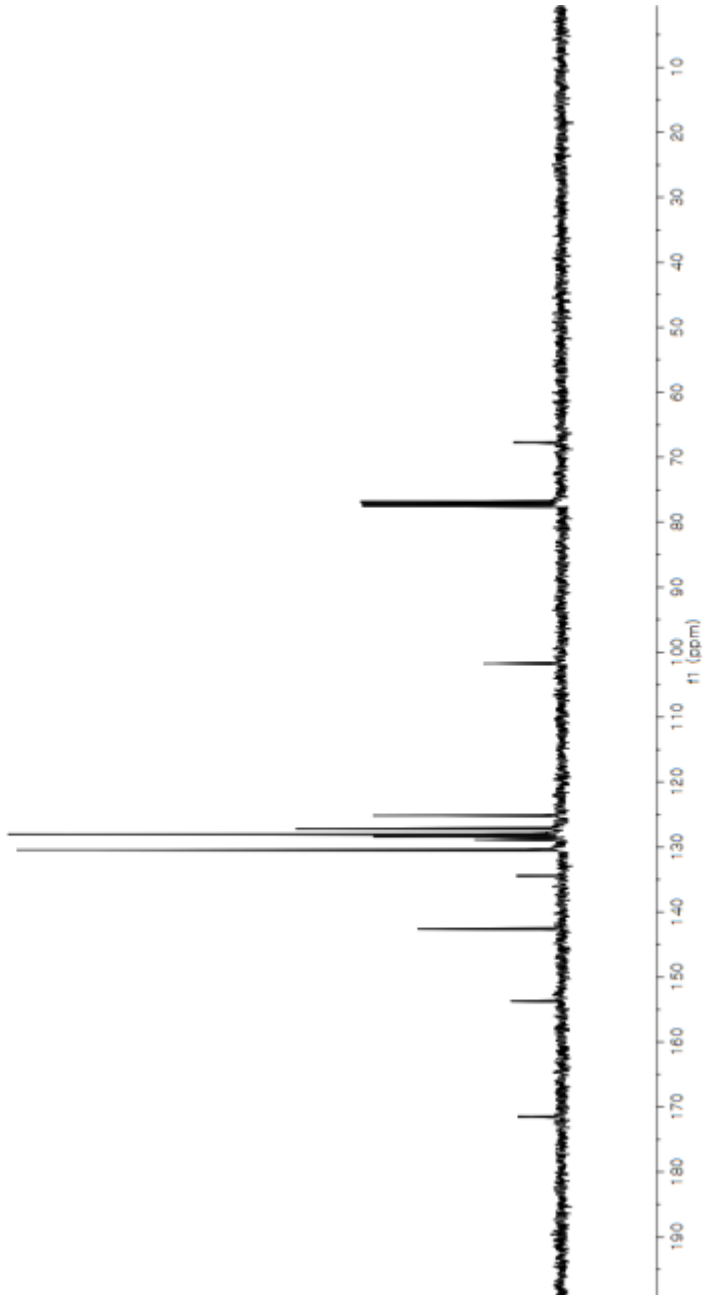
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.16 (m, 18H), 7.06 (d, J = 8.0 Hz, 2H), 5.47 (dd, J = 2.4 Hz, 2.4 Hz, 1H), 5.14 (dd, J = 2.3 Hz, 2.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 153.7, 142.6, 134.4, 130.4, 128.9, 128.4, 128.1, 127.1, 125.1, 101.7, 67.7.

LRMS (CI) Calcd. for $C_{28}H_{22}O_2$ $[M+H]^+$: 391, Found: 391.

FTIR (neat): 3060, 1747.


1.03
1.00
2.05
16.82
f1 (ppm)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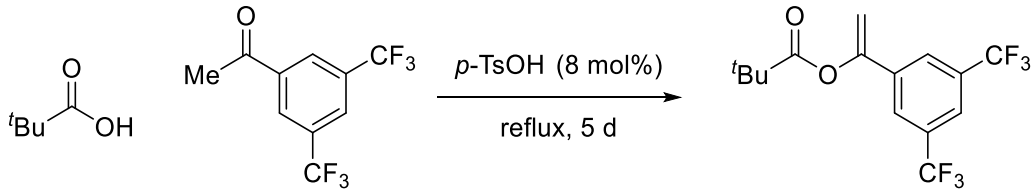
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

1-(3,5-Bis(trifluoromethyl)phenyl)vinyl pivalate (4.2e)



In modification to literature procedure,[78] a flame-dried 250 mL round-bottom flask was charged with 1-(3,5-bis(trifluoromethyl)-phenyl) ethan-1-one (15.4 mL, 95 mmol), vinyl dimethylpropionate (32 mL, 210 mmol) and *p*-toluenesulfonic acid (1.5 g, 7.8 mmol). The solution was refluxed for 5 days in 250 mL round-bottom flask. The mixture was allowed to cool to room temperature, and the mixture was concentrated. Ether was added (50 mL), and the resulting solvent was washed with water (3 x 20 mL) and dried over $MgSO_4$. The residue was purified by vacuum distillation. When the distillated compound included impurities, it was further subjected to flash column chromatography (SiO_2, 5% DCM/hexanes) to furnish the titled compound (2.3 g, 7%) as a white solid.

R_f : 0.60 (hexanes:DCM = 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 2H), 7.83 (s, 1H), 5.61 (d, J = 2.6 Hz, 1H), 5.21 (d, J = 2.6 Hz, 1H), 1.36 (s, 9H).

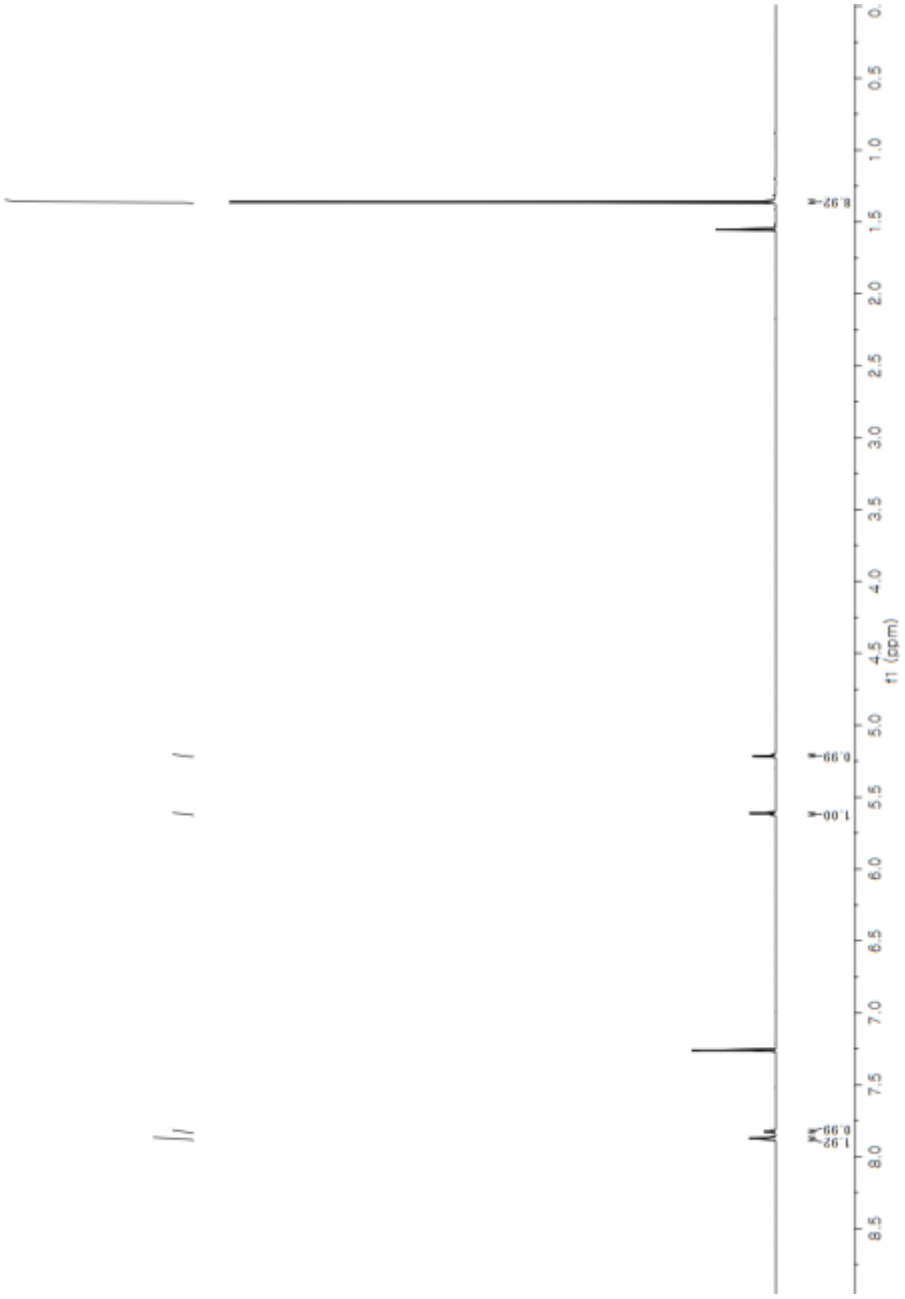
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 150.7, 137.2, 132.2 (quartet, J = 33.0 Hz), 125.0, 123.2 (quartet, J = 271.0 Hz), 122.52, 122.49, 105.3, 39.4, 27.2.

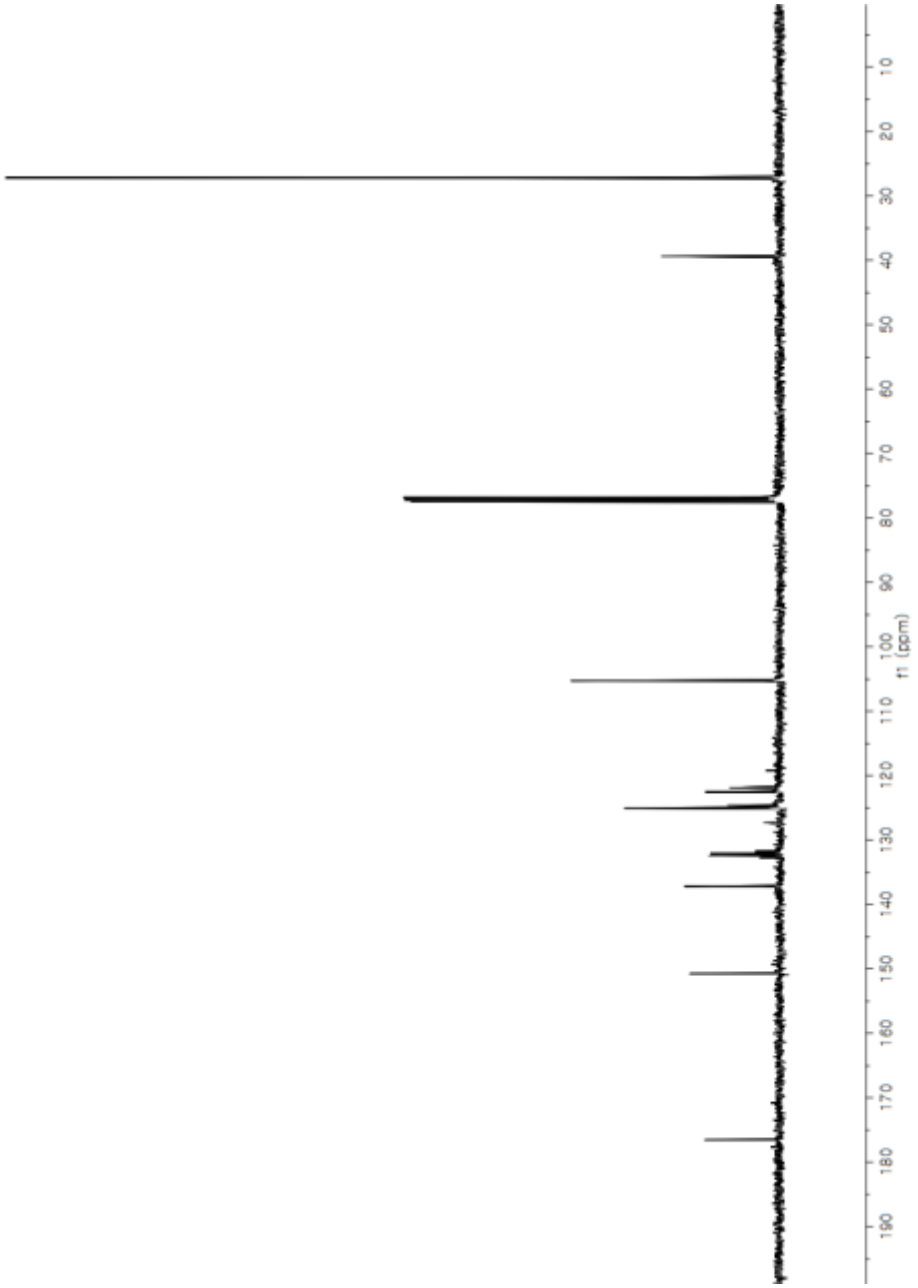
^{19}F NMR (376 MHz, $CDCl_3$): δ -63.2.

LRMS (CI) Calcd. for $C_{15}H_{14}F_6O_2$ $[M-F]^+$: 321, Found: 321.

FTIR (neat): 2360, 1744.

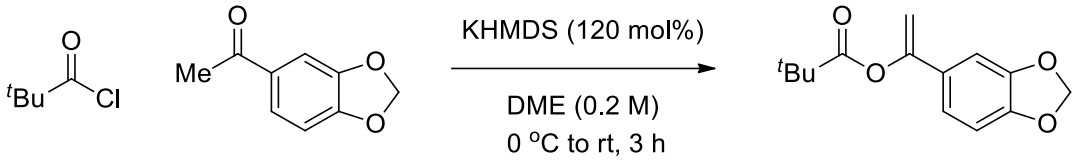
MP: 88.3–89.5 °C.


8.92
0.99
1.00
0.99
1.92
f1 (ppm)


f1 (ppm)

f1 (ppm)

1-(Benzo[*d*][1,3]dioxol-5-yl)vinyl pivalate (4.2j).



A flame-dried 50 mL round-bottom flask was charged with potassium bis(trimethylsilyl)amide (KHMDS) (2.4 g, 12 mmol) and DME (10 mL). To this stirring mixture 3',4'-(methylenedioxy)acetophenone (1.6 g, 10 mmol) was added dropwise. The resulting solution was stirred for an additional 15 min and was then transferred dropwise *via* syringe to another 50 mL round-bottom flask with pivaloyl chloride (1.2 mL, 10.0 mmol) in DME (10 mL) at 0 °C. The reaction mixture was stirred for 3 hours, and then quenched with NH_4Cl (10 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were successively washed with water (3 × 10 mL) and brine (3 × 10 mL), and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to afford the title compound (.87 g, 35%) as a white solid.

R_f: 0.27 (hexanes:DCM = 3:2).

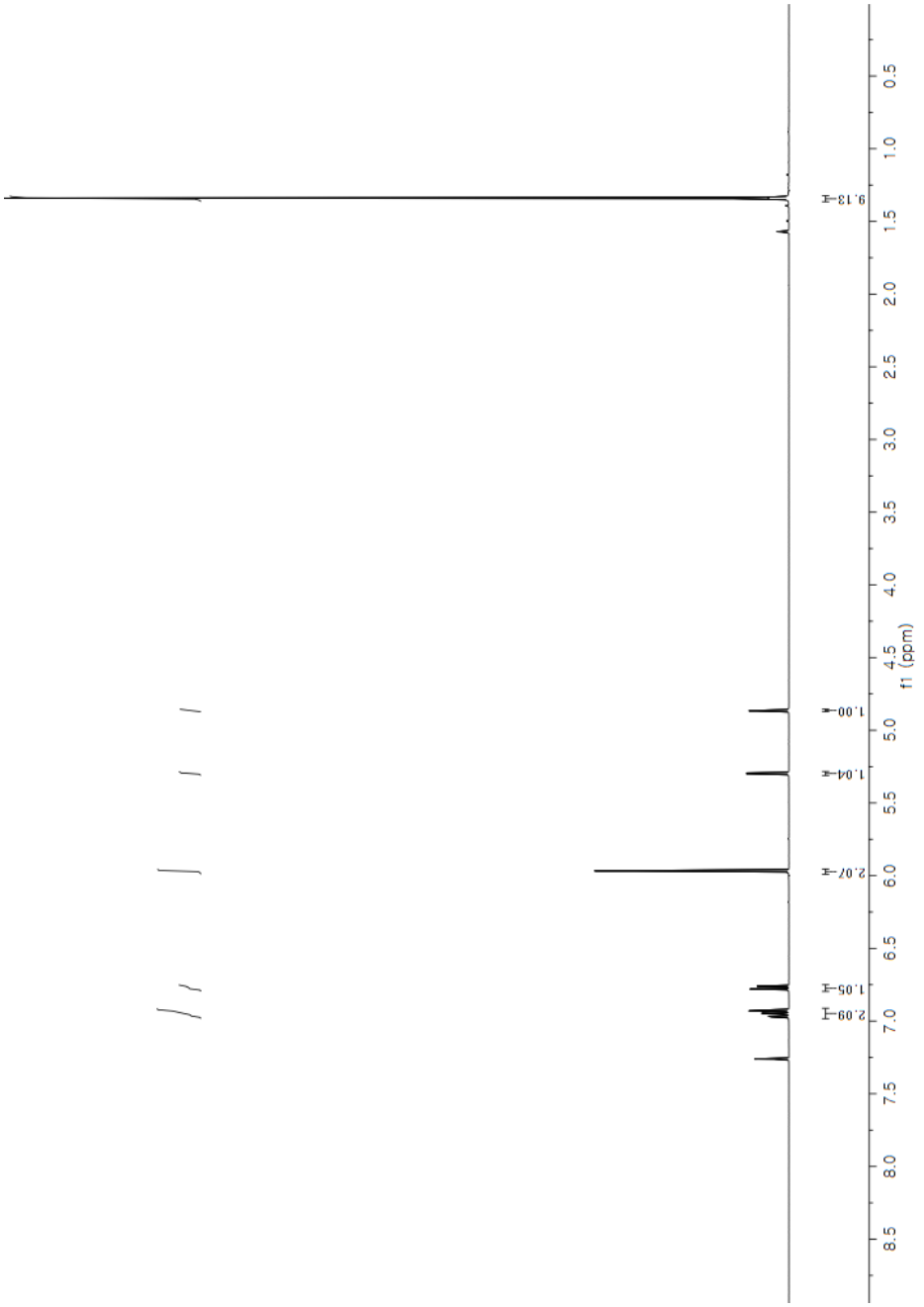
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95–6.93 (m, 2H), 6.77 (dd, *J* = 8.0 Hz, 0.4 Hz, 1H), 5.97 (s, 2H), 5.30 (d, *J* = 2.4 Hz, 1H), 4.86 (d, *J* = 2.4 Hz, 1H), 1.34 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 153.0, 148.3, 148.0, 129.2, 119.1, 108.4, 105.7, 101.4, 100.7, 39.3, 27.3.

LRMS (CI) Calcd. for $C_{14}H_{16}O_4$ $[M]^+$: 248, Found: 248.

FTIR (neat): 2979, 1746.

MP: 54.8–56.4 °C.


9.13
1.00
1.04
2.07
1.05
2.09
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
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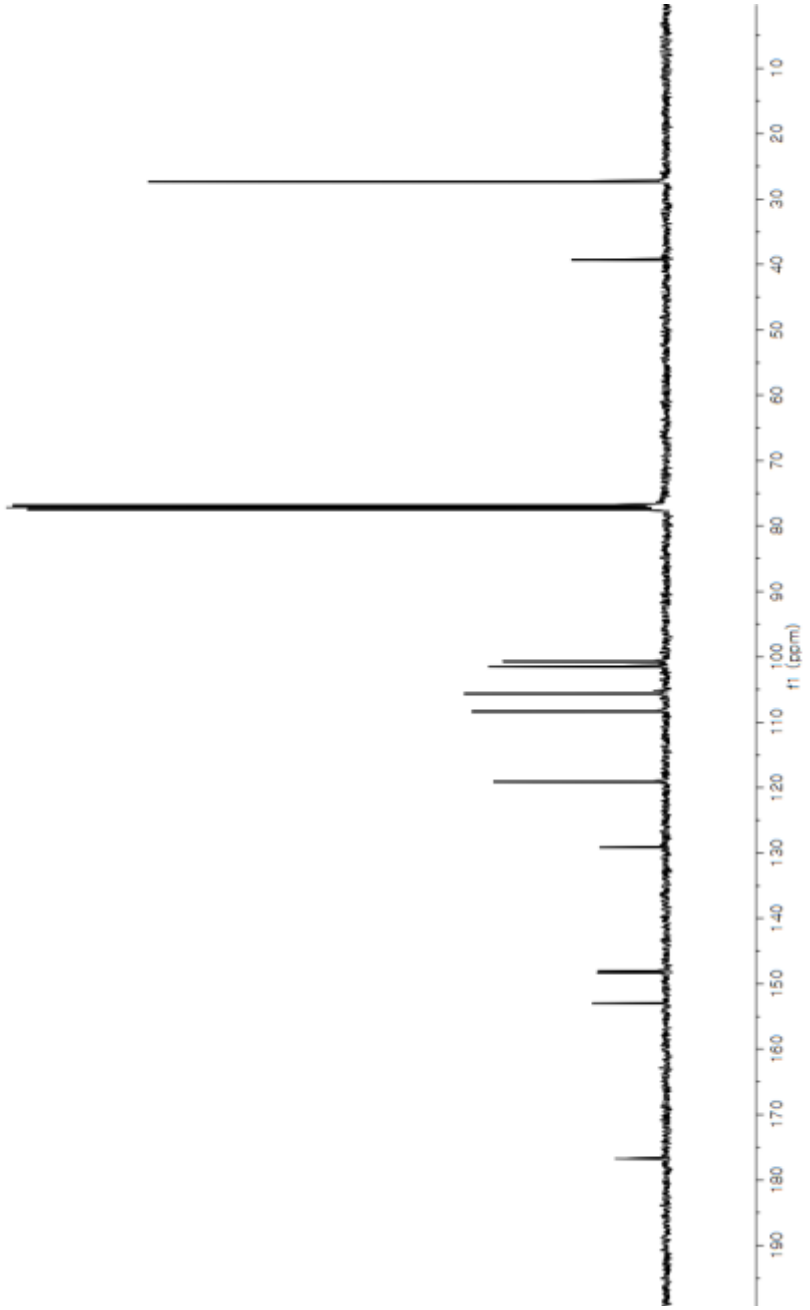
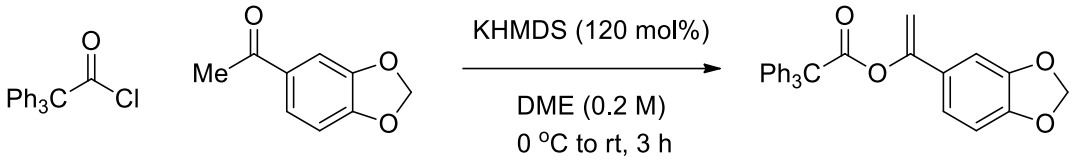
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

1-(Benzo[*d*][1,3]dioxol-5-yl)vinyl 2,2,2-triphenylacetate (4.2f)



A flame-dried 50 mL round-bottom flask was charged with potassium bis(trimethylsilyl)amide (KHMDS) (2.4 g, 12 mmol) and DME (10 mL). To this stirring mixture 3',4'-(methylenedioxy)acetophenone (1.6 g, 10 mmol) was added dropwise. The resulting solution was stirred for an additional 15 min and was then transferred dropwise *via* syringe to another 50 mL round-bottom flask with triphenylacetyl chloride (3.0 g, 9.8 mmol) in DME (10 mL) at 0 °C. The reaction mixture was stirred for 3 hours, and then quenched with NH_4Cl (10 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were successively washed with water (3 × 10 mL) and brine (3 × 10 mL), and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexanes) to afford the title compound (1.3 g, 30%) as a white solid.

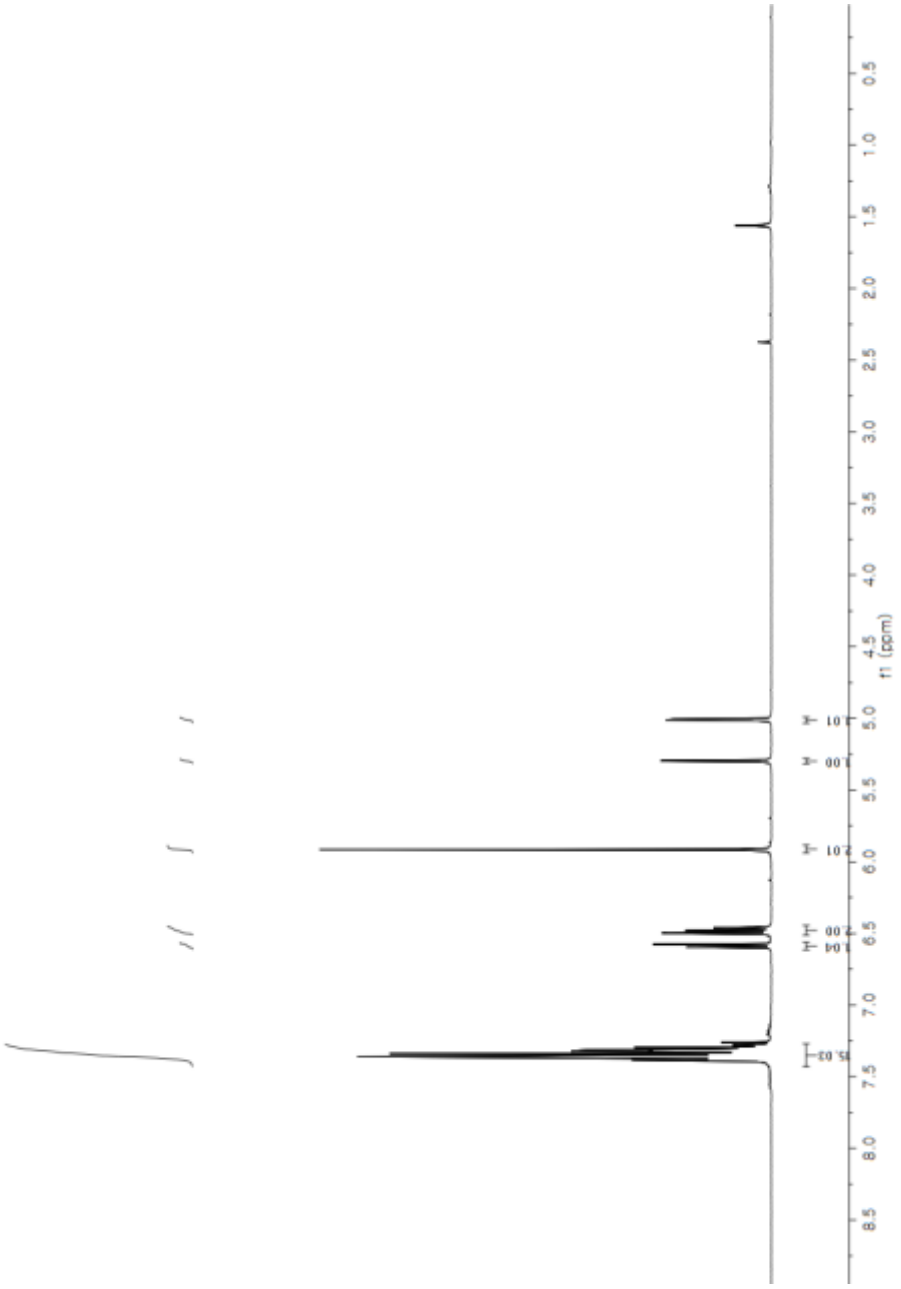
R_f: 0.27 (hexanes:DCM = 3:2).

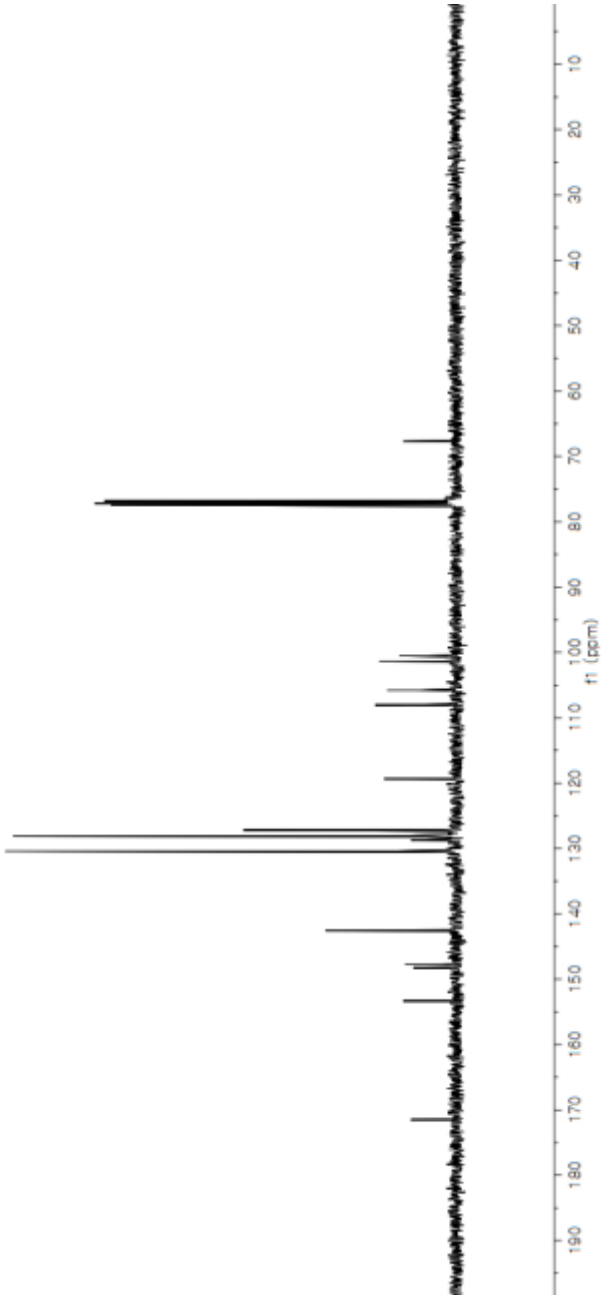
^{1}H NMR (400 MHz, $CDCl_3$): 7.43–7.27 (m, 15H), 6.59 (d, J = 8.1 Hz, 1H), 6.51–6.44 (m, 2H), 5.91 (s, 2H), 5.30 (d, J = 2.3 Hz, 1H), 5.01 (d, J = 2.3 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 153.3, 148.2, 147.8, 142.5, 130.4, 128.7, 128.1, 127.2, 119.3, 108.1, 105.8, 101.3, 100.5, 67.7.

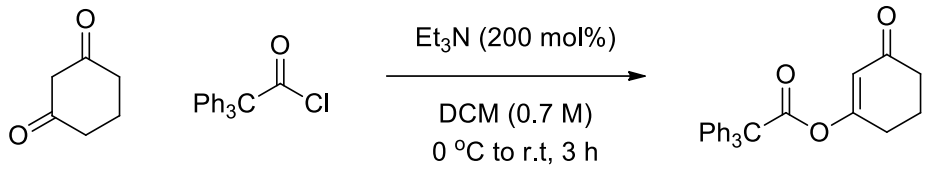
LRMS (ESI) Calcd. for $C_{29}H_{22}O_4$ $[M+Na]^+$: 457, Found: 457.

FTIR (neat): 2970, 2360, 1741.


f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

3-Oxocyclohex-1-en-1-yl 2,2,2-triphenylacetate (4.2k)



A flame-dried 25 mL round-bottom flask was charged with 1,3-cyclohexanedione (305 mg, 2.7 mmol), trimethylamine (0.76 mL, 5.4 mmol) and DCM (4 mL). To this stirring mixture 2,2,2-triphenylacetyl chloride (900 mg, 2.9 mmol) was added at 0 °C. The resulting solution was stirred for an additional 3 hours at r.t, and then quenched with water (5 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were successively washed with water (3 × 10 mL) and brine (3 × 10 mL), and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 20% EtOAc/hexanes) to afford the title compound (855 mg, 82%) as a white solid.

R_f : 0.22 (EtOAc:hexanes = 1:4).

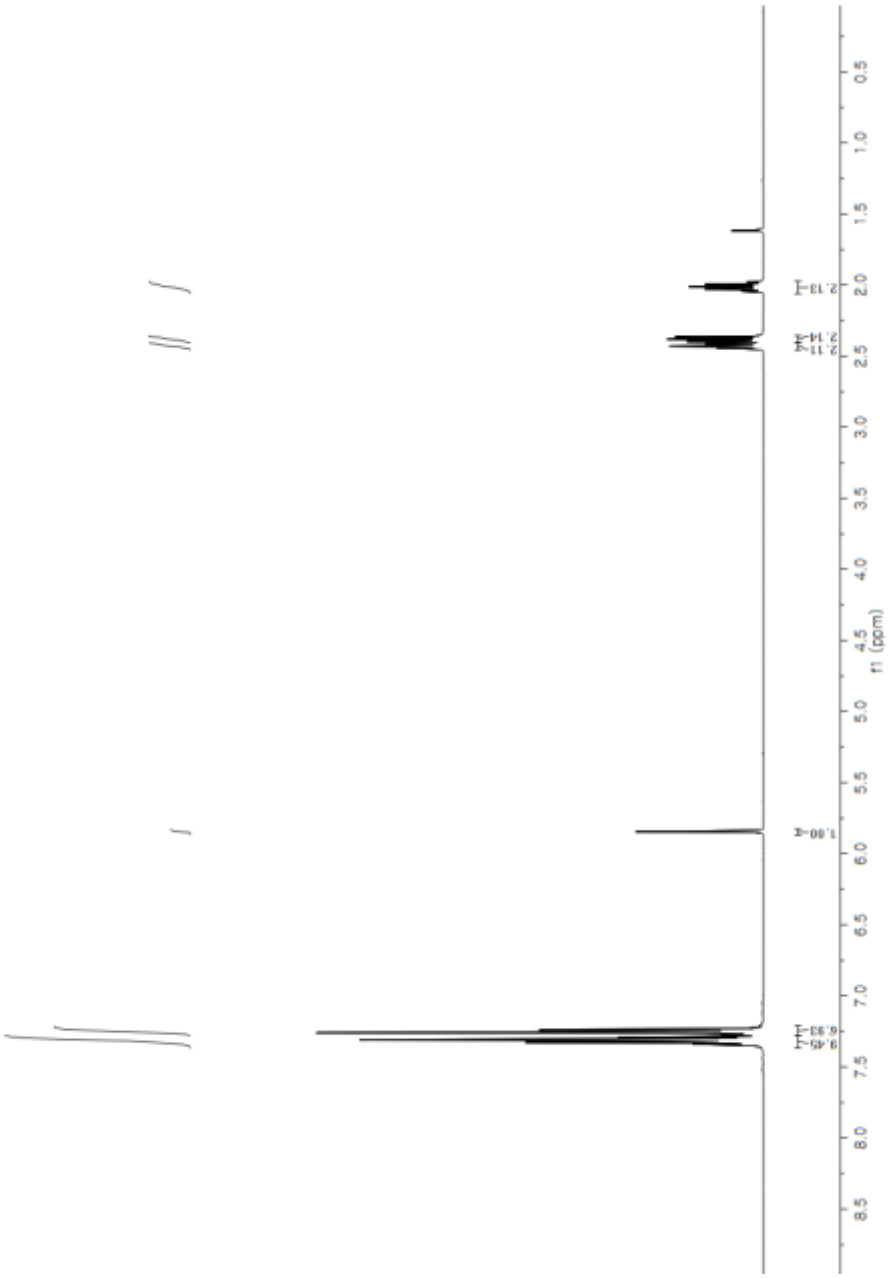
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.23 (m, 15H), 5.84 (t, *J* = 1.2 Hz, 1H), 2.43 (td, *J* = 6.2 Hz, 1.2 Hz, 2H), 2.40–2.36 (m, 2H), 2.04–1.98 (m, 2H).

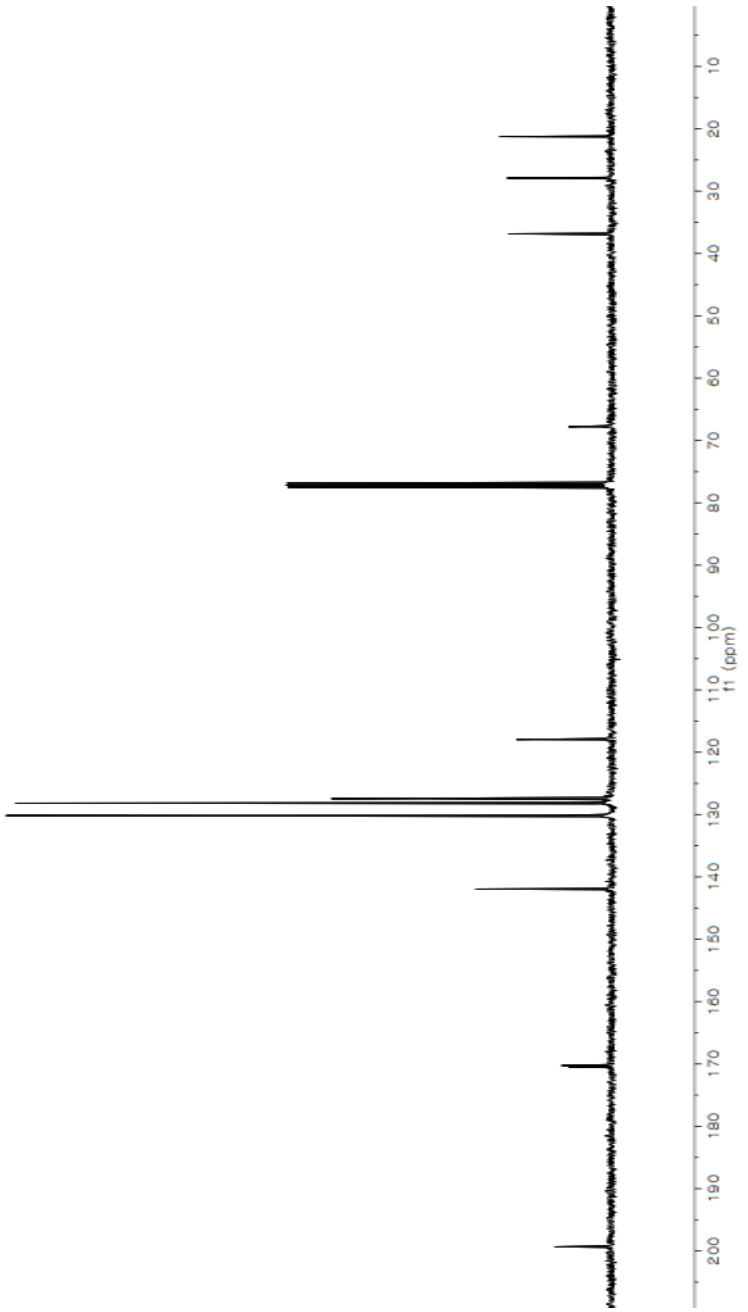
^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 170.5, 170.3, 141.9, 130.2, 128.2, 127.4, 118.0, 67.8, 36.8, 27.9, 21.3.

LRMS (ESI) Calcd. for $C_{26}H_{22}O_3$ $[M+Na]^+$: 405, Found: 405.

FTIR (neat): 3052, 1746, 1675.

MP: 159.6-160.2 °C.


2.13
2.11
2.14
1.00
9.45
6.93
f1 (ppm)

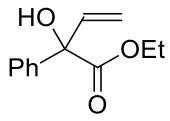

f1 (ppm)

General Procedure for Carbinol C-H Activation:

(For solid alcohol coupling partners): A resealable pressure tube (ca. 13 x 100) was charged with M_3CO_{12} (3.9 mg of Ru_3CO_{12} or 5.5 mg of Os_3CO_{12}, 0.006 mmol, 2 mol%), XPhos (17.7 mg, 0.036 mmol, 12 mol%), and the reactant alcohol (0.30 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with argon. Toluene (0.15 mL, 2.0 M with respect to the alcohol reactant) was added. The enol carboxylate (0.90 mmol, 300 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The mixture was heated at the temperature stated for the time stated. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the desired product.

(For liquid alcohol coupling partners): A resealable pressure tube (ca. 13 x 100) was charged with M_3CO_{12} (3.9 mg of Ru_3CO_{12} or 5.5 mg of Os_3CO_{12}, 0.006 mmol, 2 mol%), XPhos (17.7 mg, 0.036 mmol, 12 mol%), and the reactant alcohol (0.30 mmol, 100 mol%). The tube was sealed with a rubber septum and purged with argon. Toluene (0.15 mL, 2.0 M with respect to the alcohol reactant) was added. The reactant alcohol (0.30 mmol, 100 mol%) and the enol carboxylate (0.90 mmol, 300 mol%) was added *via* syringe and the rubber septum was quickly replaced with a screw cap. The mixture was heated at the temperature stated for the time stated. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2) under the conditions noted to afford the desired product.

Ethyl 2-hydroxy-2-phenylbut-3-enoate (4.3a)



The reaction was conducted at 140 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 2% EtOAc/hexanes to 4% EtOAc/hexanes) provided the title compound (51.4 mg, 83%) as a pale yellow oil.

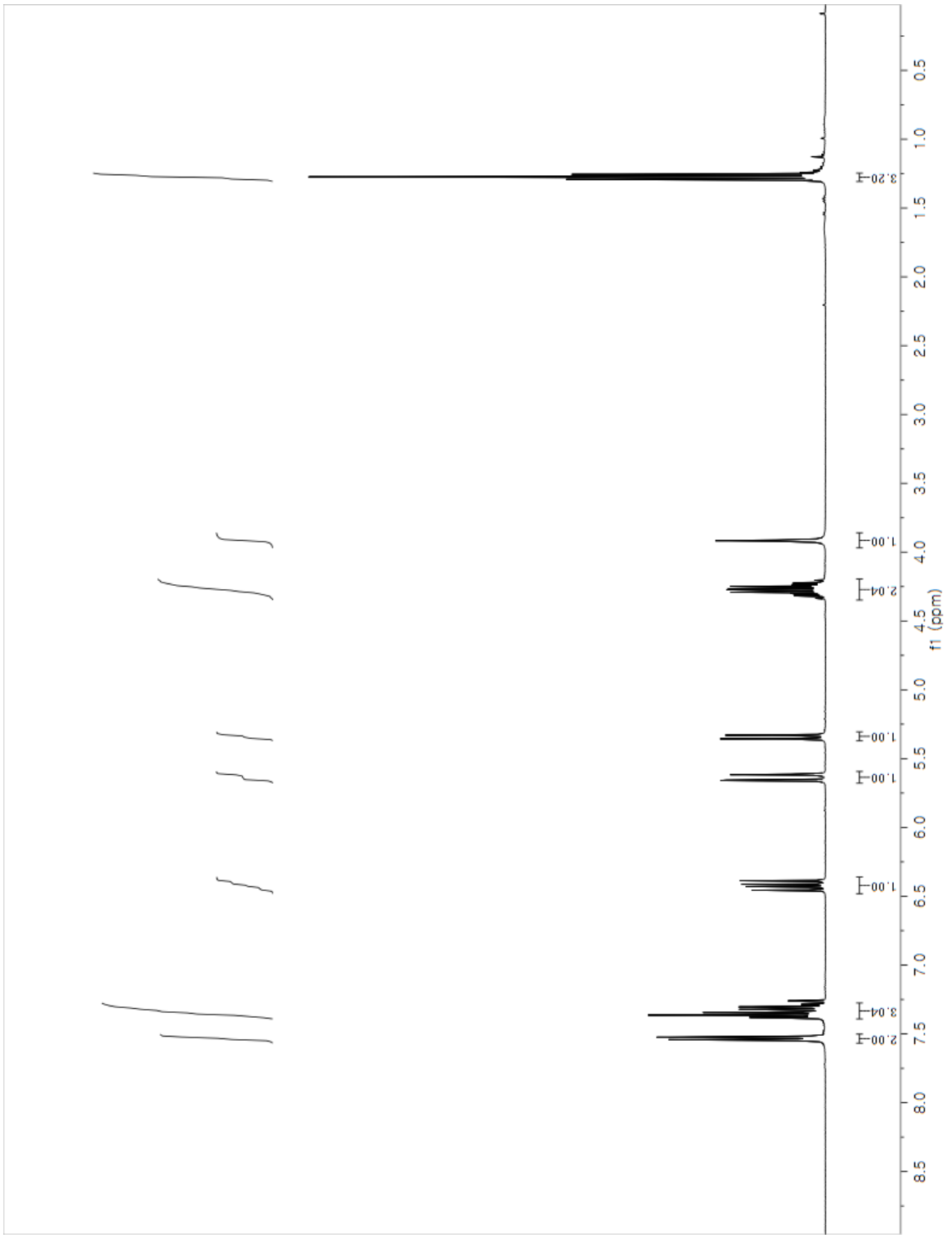
R_f: 0.49 (EtOAc:hexanes = 1:4).

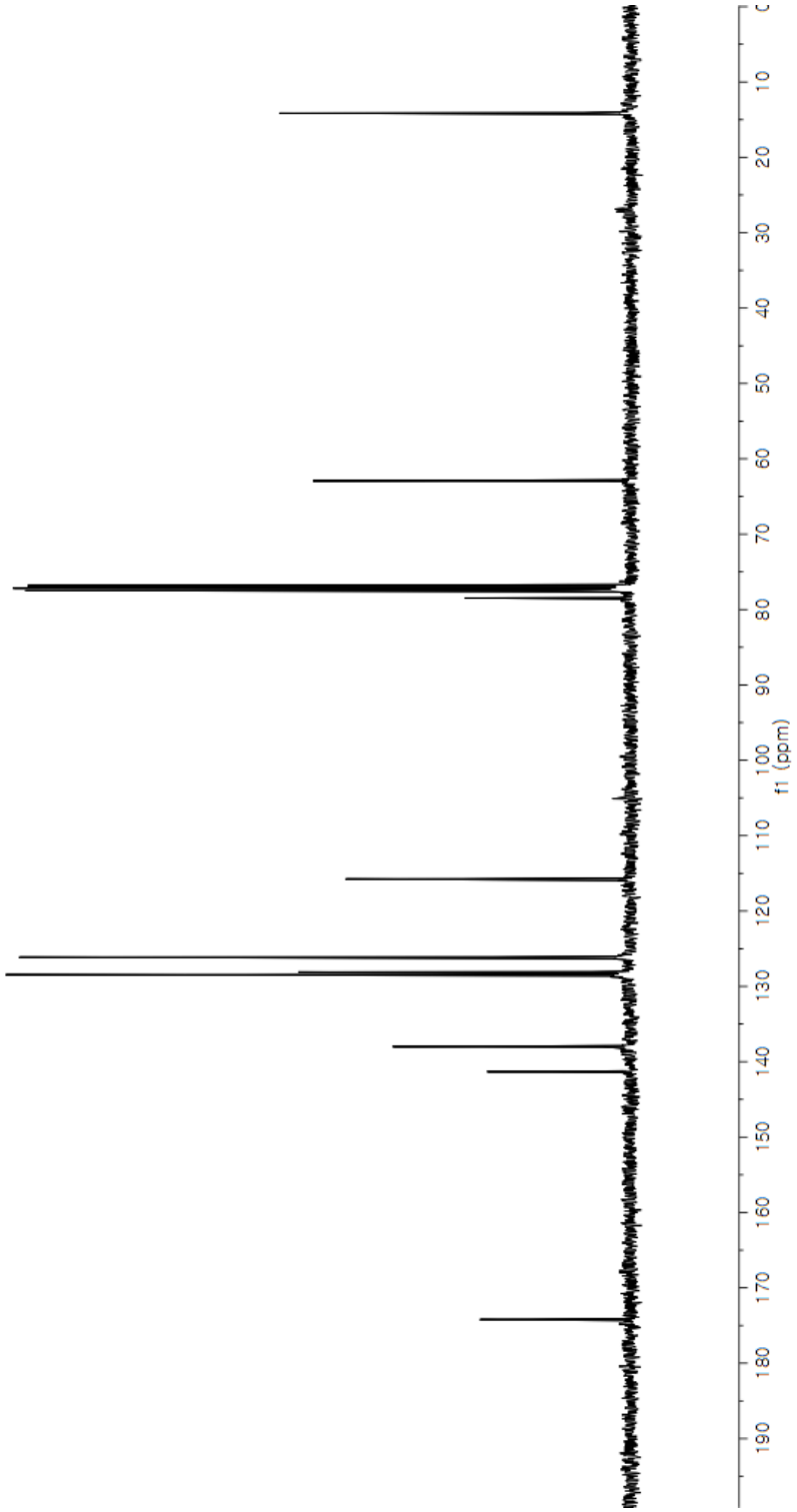
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.52 (m, 2H), 7.38–7.28 (m, 3H), 6.42 (dd, *J* = 17.0 Hz, 10.6 Hz, 1H), 5.64 (dd, *J* = 16.8 Hz, 1.2 Hz, 1H), 5.34 (dd, *J* = 10.4 Hz, 1.2 Hz, 1H), 4.34–4.20 (m, 2H), 3.92 (s, 1H), 1.27 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 141.3, 138.0, 128.5, 128.1, 126.1, 115.8, 78.5, 62.9, 14.1.

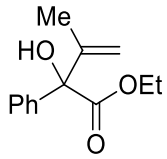
LRMS (ESI) Calcd. for $C_{12}H_{14}O_3$ $[M+Na]^+$: 229, Found: 229.

FTIR (neat): 3501, 2984, 1724.


3.20
1.00
2.04
1.00
1.00
1.00
3.04
2.00
f1 (ppm)


f1 (ppm)

Ethyl 2-hydroxy-3-methyl-2-phenylbut-3-enoate (4.3b)



Using Prop-1-en-2-yl 2,2,2-triphenylacetate (*O*-TPA-2b)

The reaction was conducted at 150 °C for a 40 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 2% EtOAc/hexanes to 3% EtOAc/hexanes) provided the title compound (52.9 mg, 80%) as a pale yellow oil.

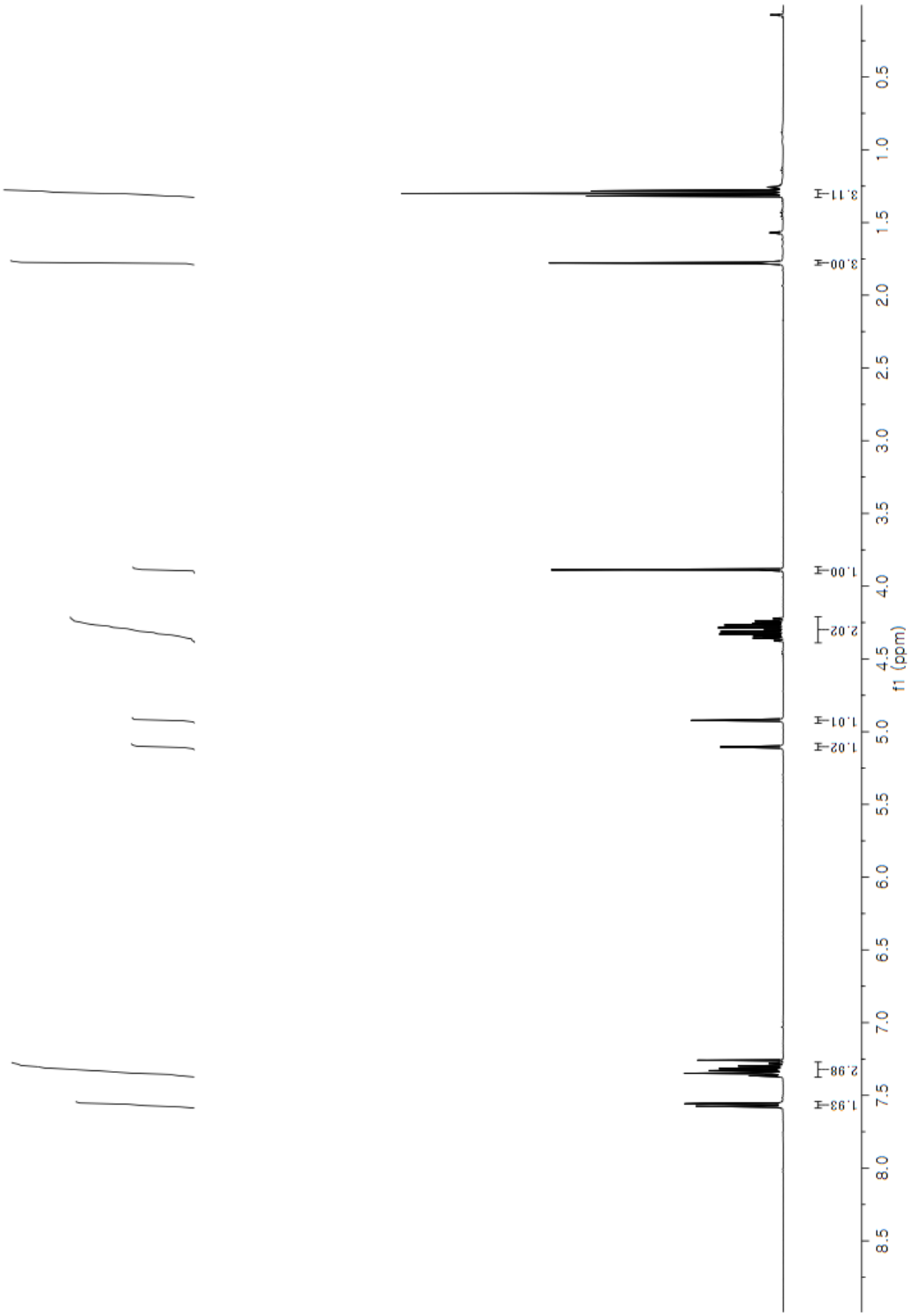
R_f: 0.51 (EtOAc:hexanes = 1:4).

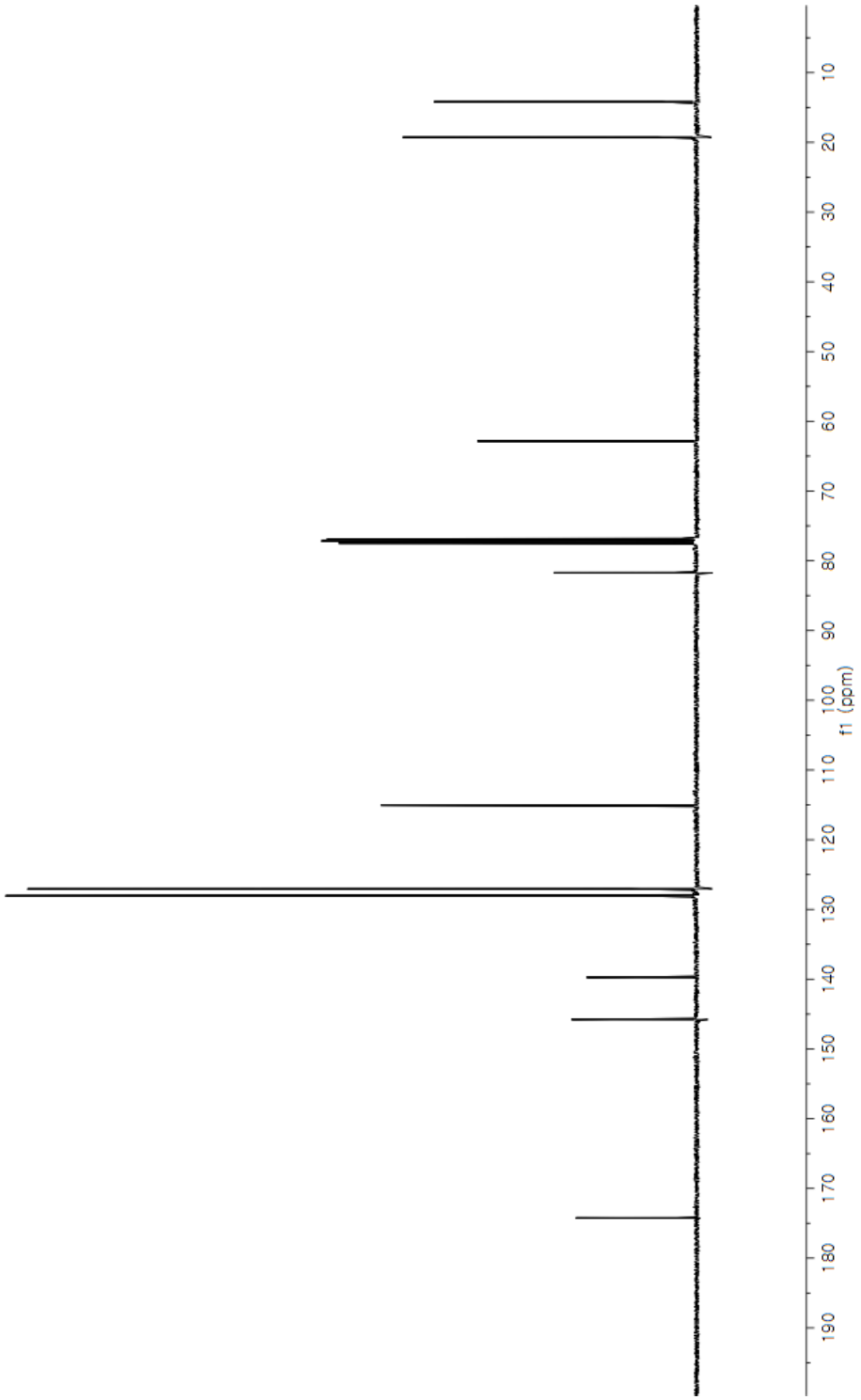
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58–7.55 (m, 2H), 7.37–7.28 (m, 3H), 5.11–5.10 (m, 1H), 4.92 (dd, J = 0.8 Hz, 0.8 Hz, 1H), 4.37–4.22 (m, 2H), 3.89 (d, J = 2.0 Hz, 1H), 1.78 (dd, J = 1.2 Hz, 0.8 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 145.8, 139.7, 128.04, 127.97, 127.1, 115.0, 81.7, 62.8, 19.3, 14.2.

LRMS (ESI) Calcd. for $C_{13}H_{16}O_3$ $[M+Na]^+$: 243, Found: 243.

FTIR (neat): 3495, 2981, 1721.


3.11
3.00
1.00
2.02
1.01
1.02
2.98
1.93
f1 (ppm)


10
20
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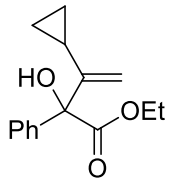
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

Ethyl 3-cyclopropyl-2-hydroxy-2-phenylbut-3-enoate (4.3c)



The reaction was conducted at 140 °C for a 40 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 2% EtOAc/hexanes to 2.5% EtOAc/hexanes) provided the title compound (48.0 mg, 65%) as a pale yellow oil.

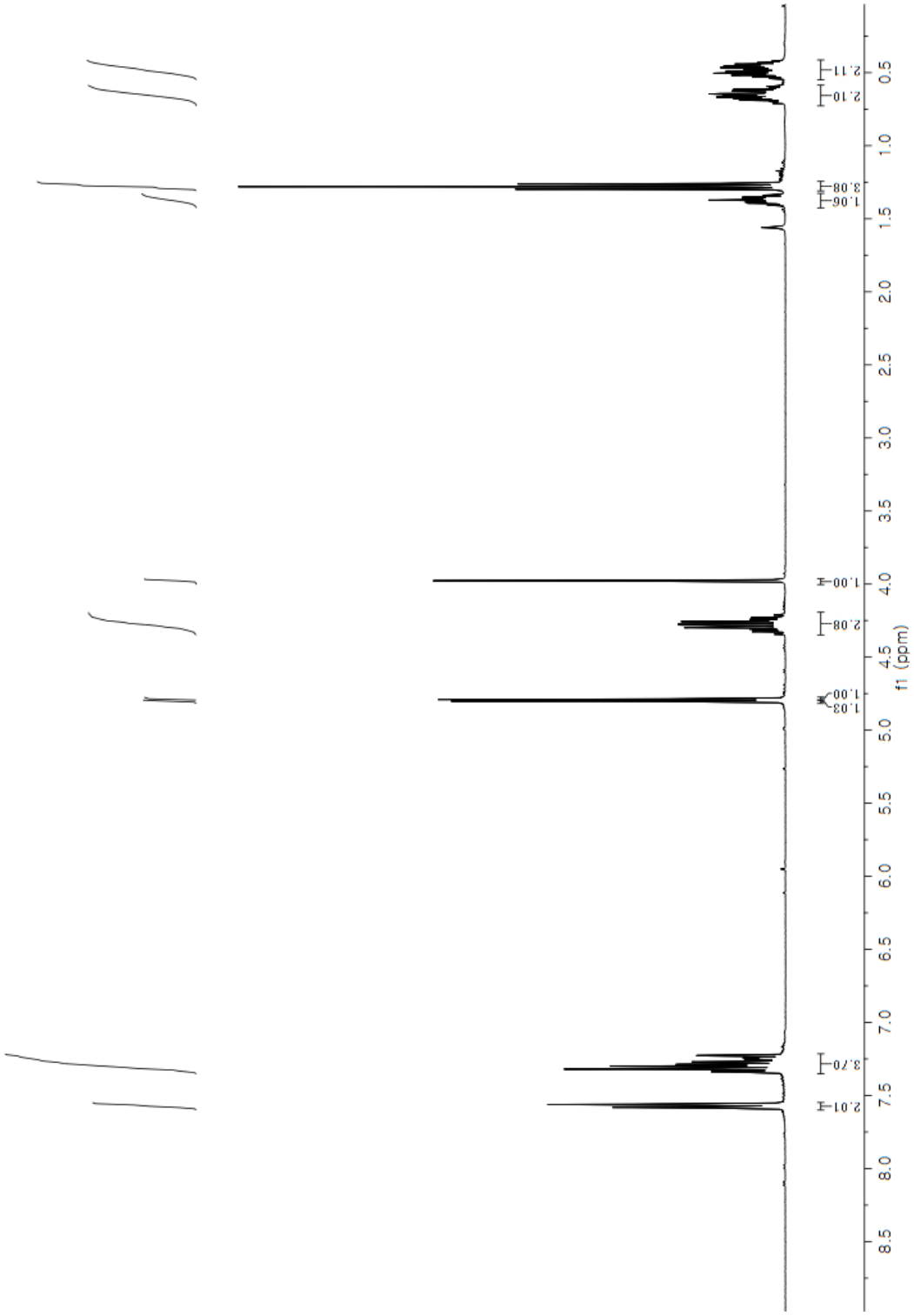
R_f: 0.60 (EtOAc:hexanes = 1:4).

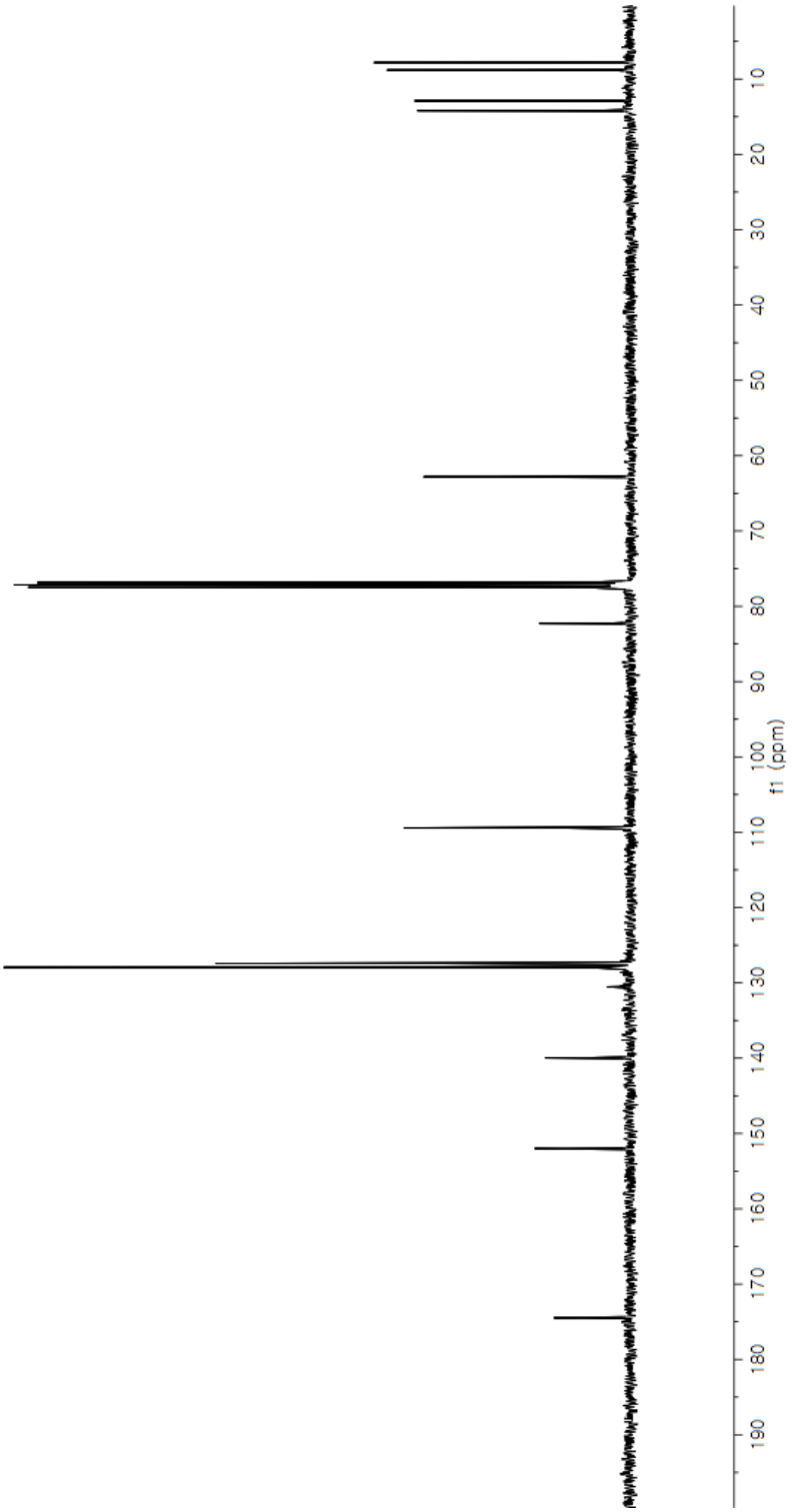
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59–7.56 (m, 2H), 7.34–7.23 (m, 3H), 4.80 (s, 1H), 4.79 (d, *J* = 0.8 Hz, 1H), 4.34–4.21 (m, 2H), 3.98 (d, *J* = 1.2 Hz, 1H), 1.41–1.34 (m, 1H), 1.28 (td, *J* = 7.2 Hz, 1.2 Hz, 3H), 0.71–0.59 (m, 2H), 0.54–0.42 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 152.0, 140.0, 130.5, 128.0, 127.4, 109.4, 82.3, 62.8, 14.2, 12.9, 8.8, 7.8.

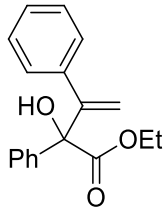
LRMS (CI) Calcd. for $C_{15}H_{18}O_3$ $[M\text{-}OH]^+$: 229, Found: 229.

FTIR (neat): 3497, 1721.


2.11
2.10
3.08
1.06
1.00
2.08
1.03
1.00
3.70
2.01
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

Ethyl 2-hydroxy-2,3-diphenylbut-3-enoate (4.3d)



The reaction was conducted at 150 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 40% DCM/hexanes to 60% DCM/hexanes) provided the title compound (60.1 mg, 71%) as a pale yellow oil.

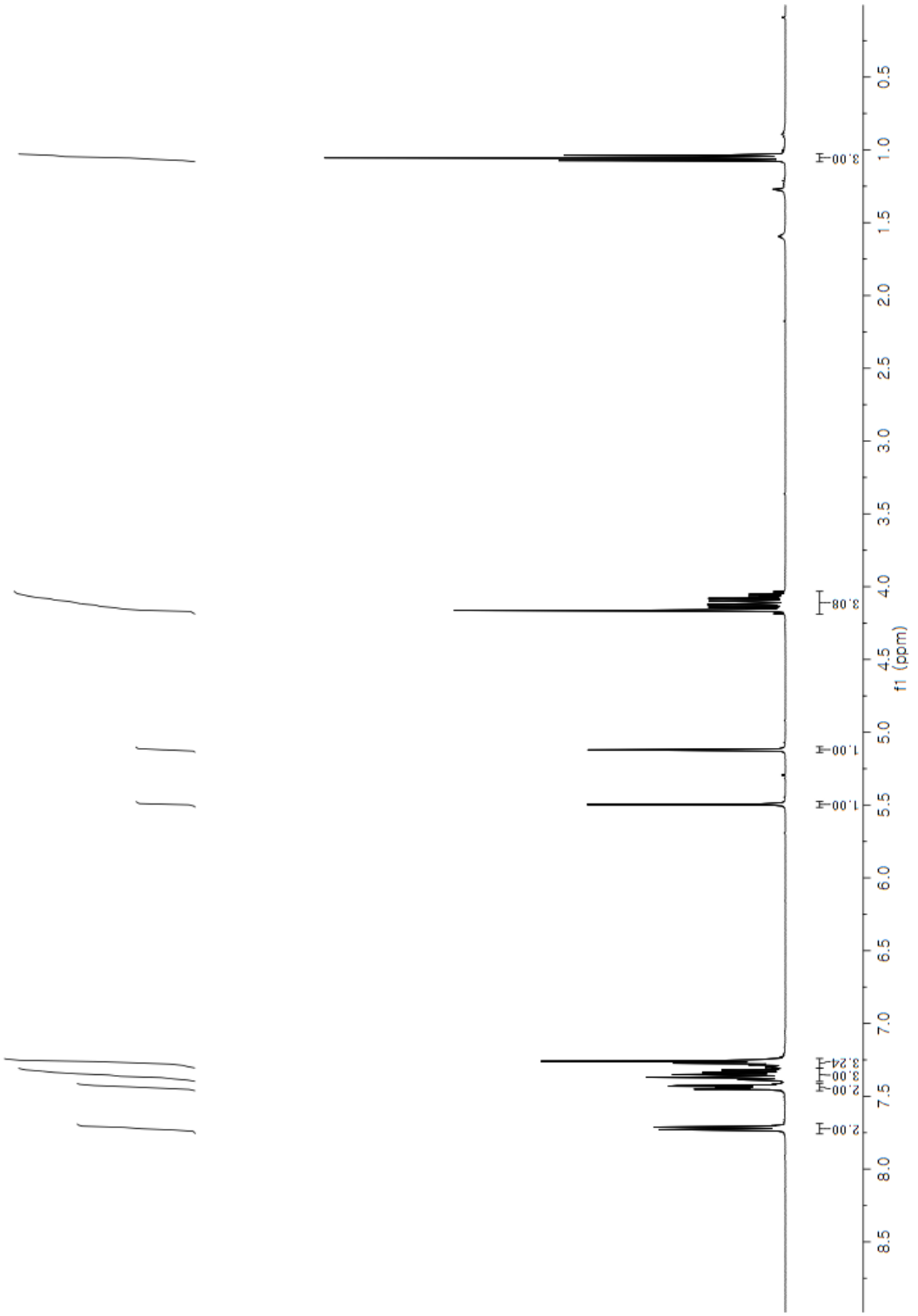
R_f: 0.49 (EtOAc:hexanes = 1:4).

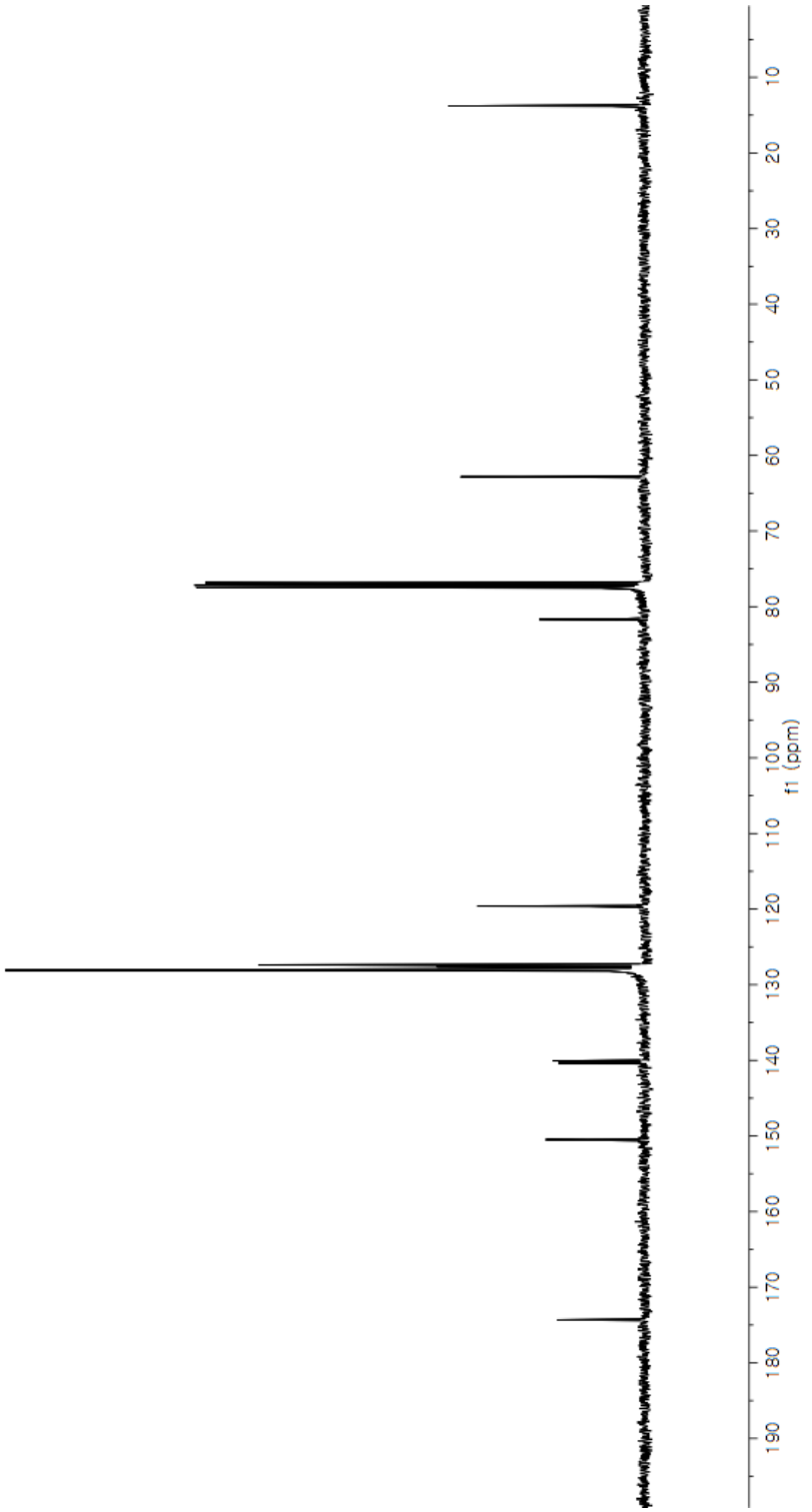
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.71 (m, 2H), 7.45–7.43 (m, 2H), 7.39–7.30 (m, 3H), 7.28–7.25 (m, 3H), 5.50 (d, J = 0.4 Hz, 1H), 5.12 (d, J = 0.4 Hz, 1H), 4.17–4.05 (m, 3H), 1.05 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 150.5, 140.3, 140.1, 128.1, 128.02, 127.98, 127.6, 127.4, 119.6, 81.7, 62.8, 13.8.

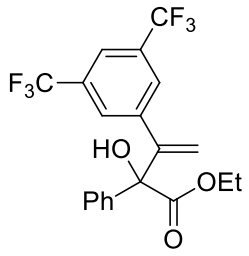
LRMS (ESI) Calcd. for $C_{18}H_{18}O_3$ $[M+Na]^+$: 305, Found: 305.

FTIR (neat): 3483, 2980, 1721.


3.00
3.08
1.00
1.00
3.24
3.00
2.00
2.00
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)



Ethyl 3-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-2-phenylbut-3-enoate (4.3e)



The reaction was conducted at 150 °C for a 48 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 30% DCM/hexanes to 35% DCM/hexanes) provided the title compound (100.4 mg, 80%) as a pale yellow oil.

R_f: 0.22 (EtOAc:hexanes = 1:4).

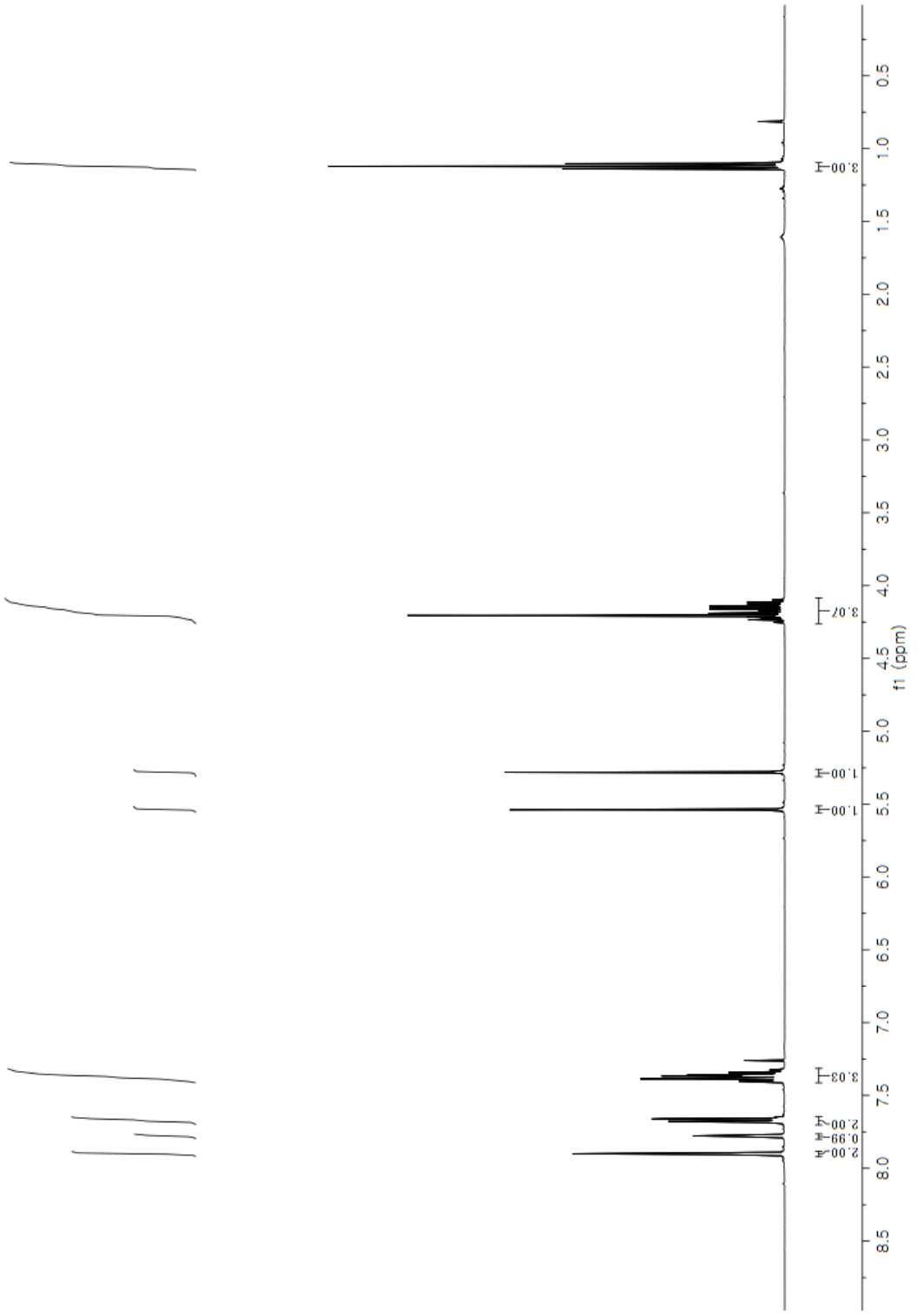
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (s, 2H), 7.78 (s, 1H), 7.68–7.65 (m, 2H), 7.40–7.34 (m, 3H), 5.54 (s, 1H), 5.28 (s, 1H), 4.25–4.10 (m, 3H), 1.12 (t, J = 7.2 Hz, 3H).

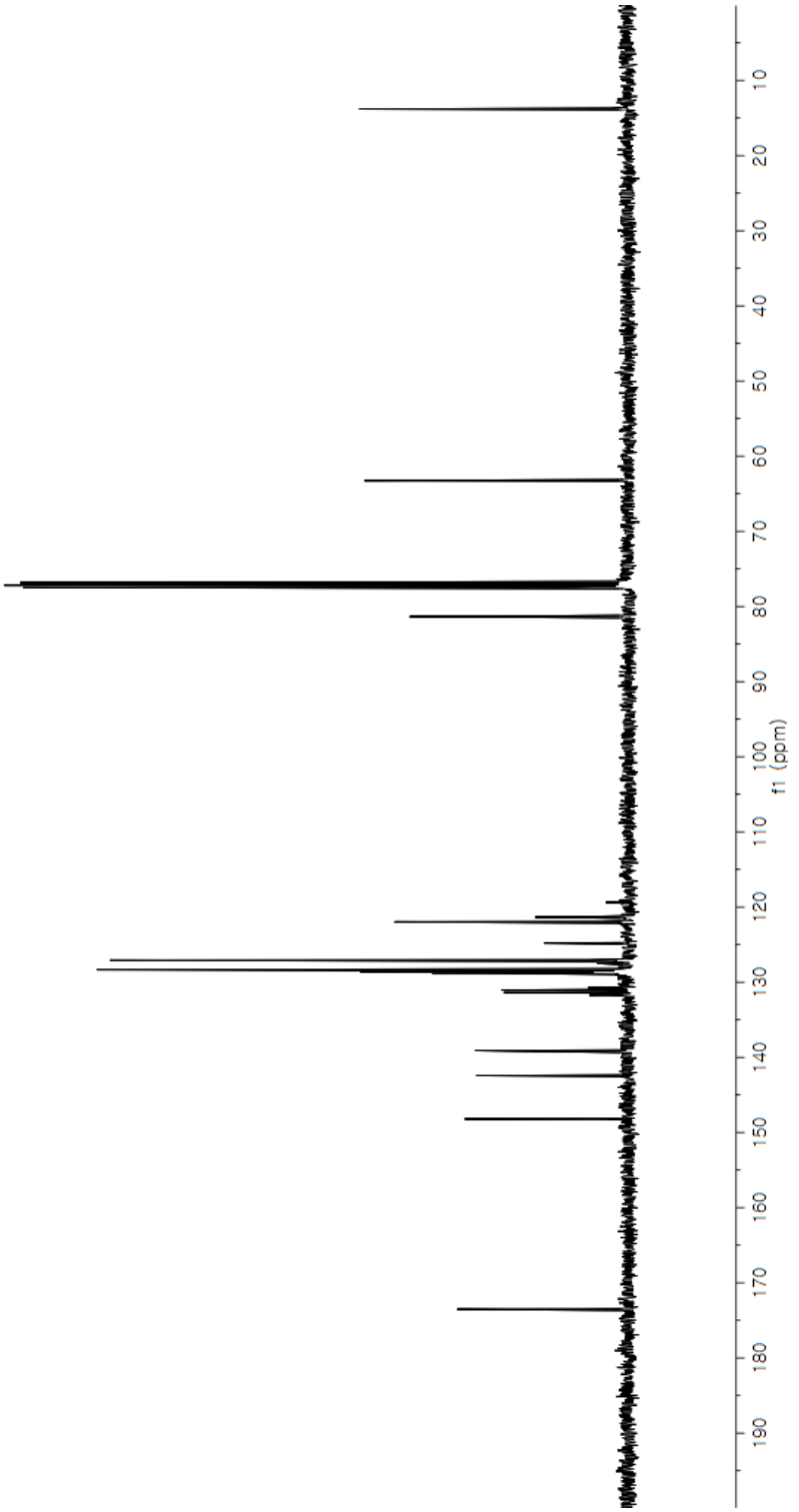
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 148.2, 142.4, 139.1, 131.2 (quartet, J = 33.0 Hz), 128.8, 128.6, 128.3, 127.1, 126.2 (quartet, J = 271.3 Hz), 122.0, 121.3, 81.4, 63.3, 13.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0.

LRMS (CI) Calcd. for $C_{20}H_{16}F_6O_3$ $[M\text{-}OH]^+$: 401, Found: 401.

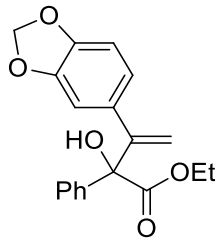
FTIR (neat): 3482, 1728.


3.00
3.07
1.00
1.00
3.03
2.00
0.99
2.00
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
f1 (ppm)

Ethyl 3-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxy-2-phenylbut-3-enoate (4.3f)



The reaction with Os_3CO_{12} (10.9 mg, 4 mol%) and XPhos (35.4 mg, 24 mol%) was conducted at 150 °C for a 72 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 4% EtOAc/hexanes) provided the title compound (44.1 mg, 45%) as a pale yellow oil and starting material was recovered (27.0 mg, 50%).

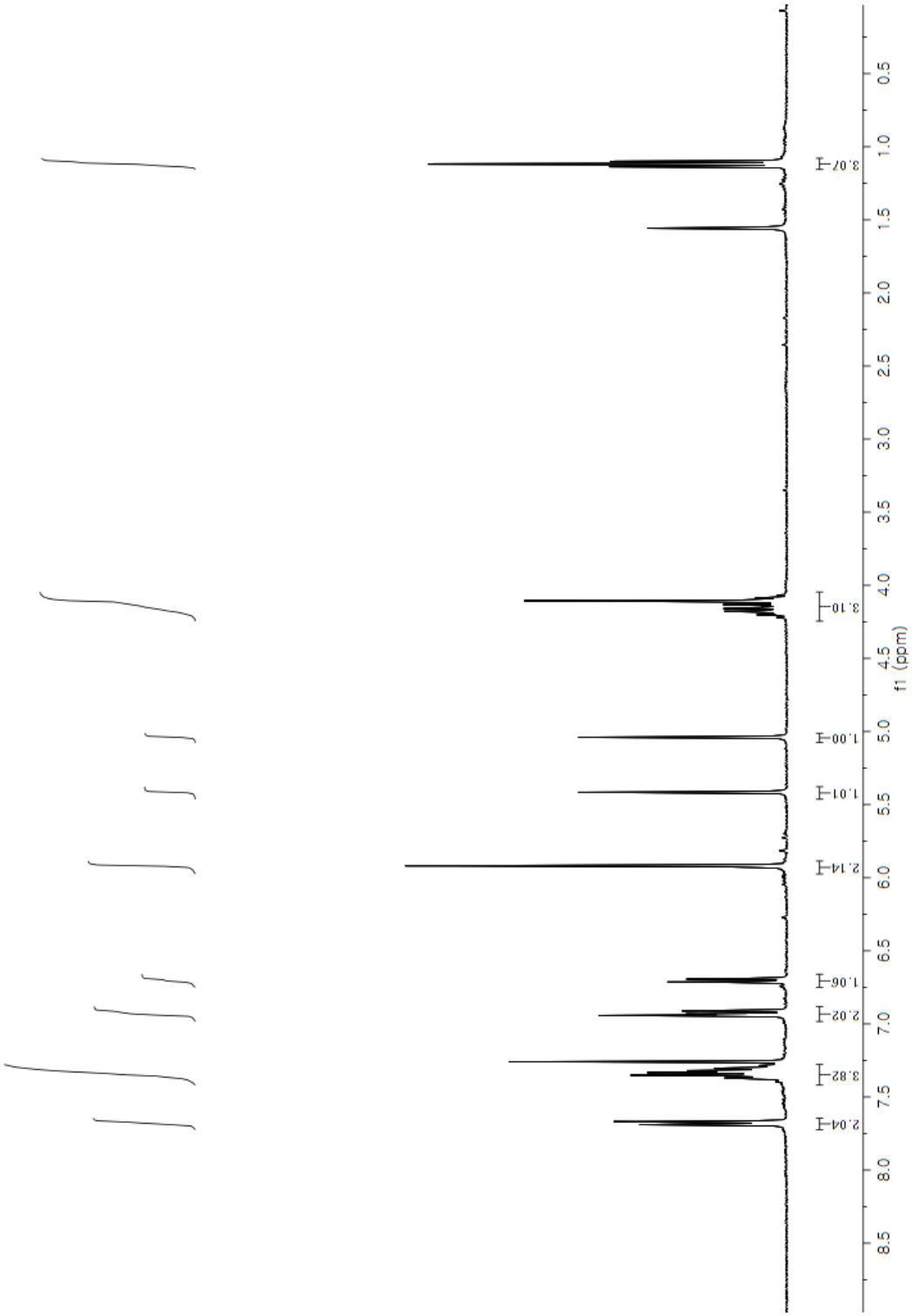
R_f: 0.31 (EtOAc:hexanes = 1:4).

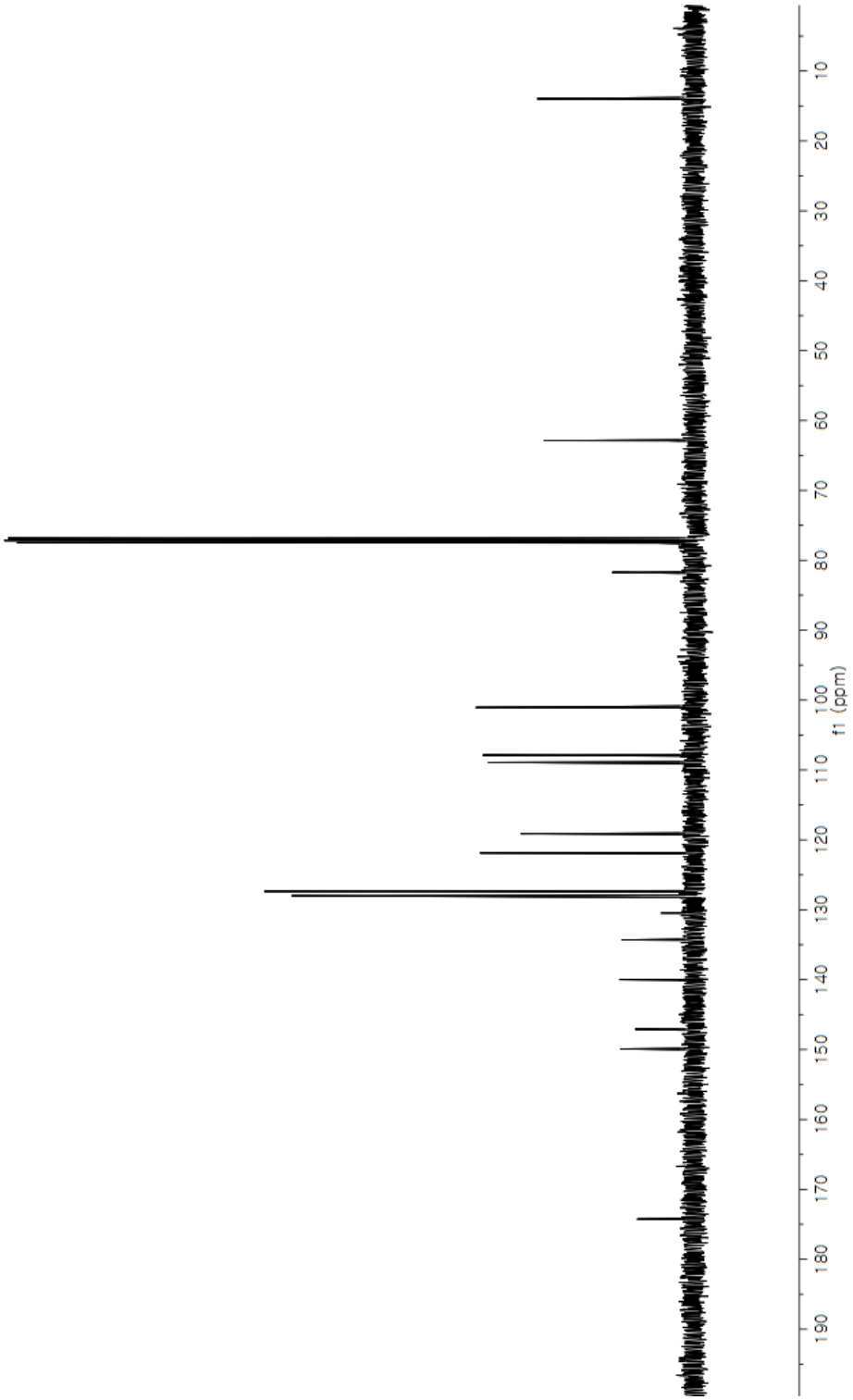
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.42–7.28 (m, 4H), 6.98–6.88 (m, 2H), 6.70 (dd, *J* = 8.0 Hz, 0.7 Hz, 1H), 5.97–5.89 (m, 2H), 5.42 (s, 1H), 5.04 (s, 1H), 4.25–4.05 (m, 3H), 1.12 (td, *J* = 7.1 Hz, 1.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 149.9, 147.2, 147.1, 140.0, 134.3, 128.1, 128.0, 127.4, 121.9, 119.1, 108.9, 107.9, 101.1, 81.7, 62.9, 14.0.

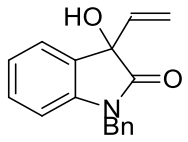
LRMS (ESI) Calcd. for $C_{19}H_{18}O_5$ $[M+Na]^+$: 349, Found: 349.

FTIR (neat): 2982, 1722.


3.07
3.10
1.00
1.01
2.14
1.06
2.02
3.82
2.04
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

1-Benzyl-3-hydroxy-3-vinylindolin-2-one (4.3g)



The reaction was conducted at 130 °C for a 4 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 10% EtOAc/hexanes to 20% EtOAc/hexanes) provided the title compound (78.8 mg, 99%) as a brown solid

R_f: 0.11 (EtOAc:hexanes = 1:4).

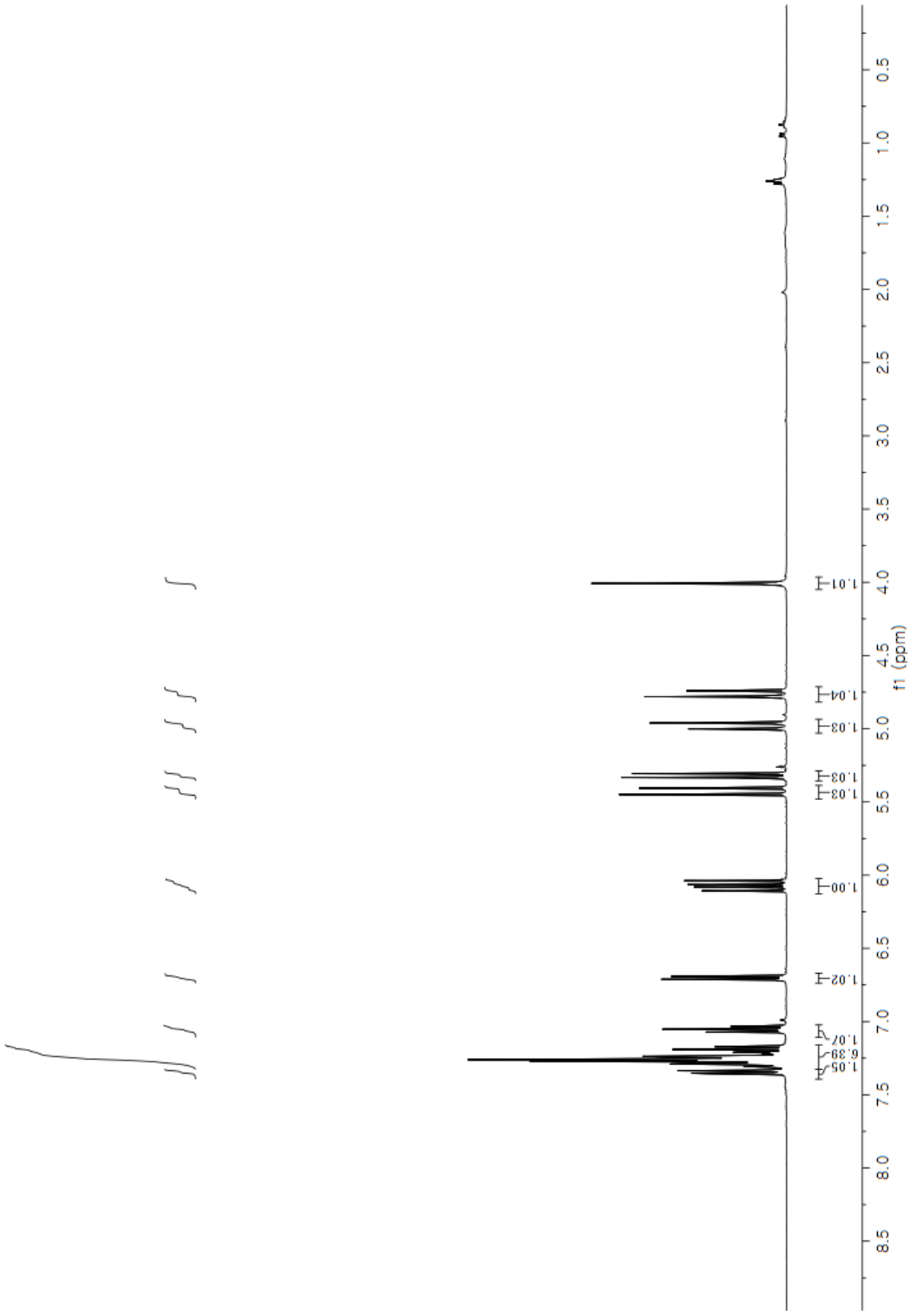
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.17 (m, 7H), 7.06 (dd, *J* = 7.2 Hz, 7.2 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 6.07 (dd, *J* = 17.0 Hz, 10.6 Hz, 1H) 5.43 (d, *J* = 17.2 Hz, 1H), 5.32 (d, *J* = 10.4 Hz, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 4.76 (d, *J* = 15.6 Hz, 1H), 4.01 (s, 1H).

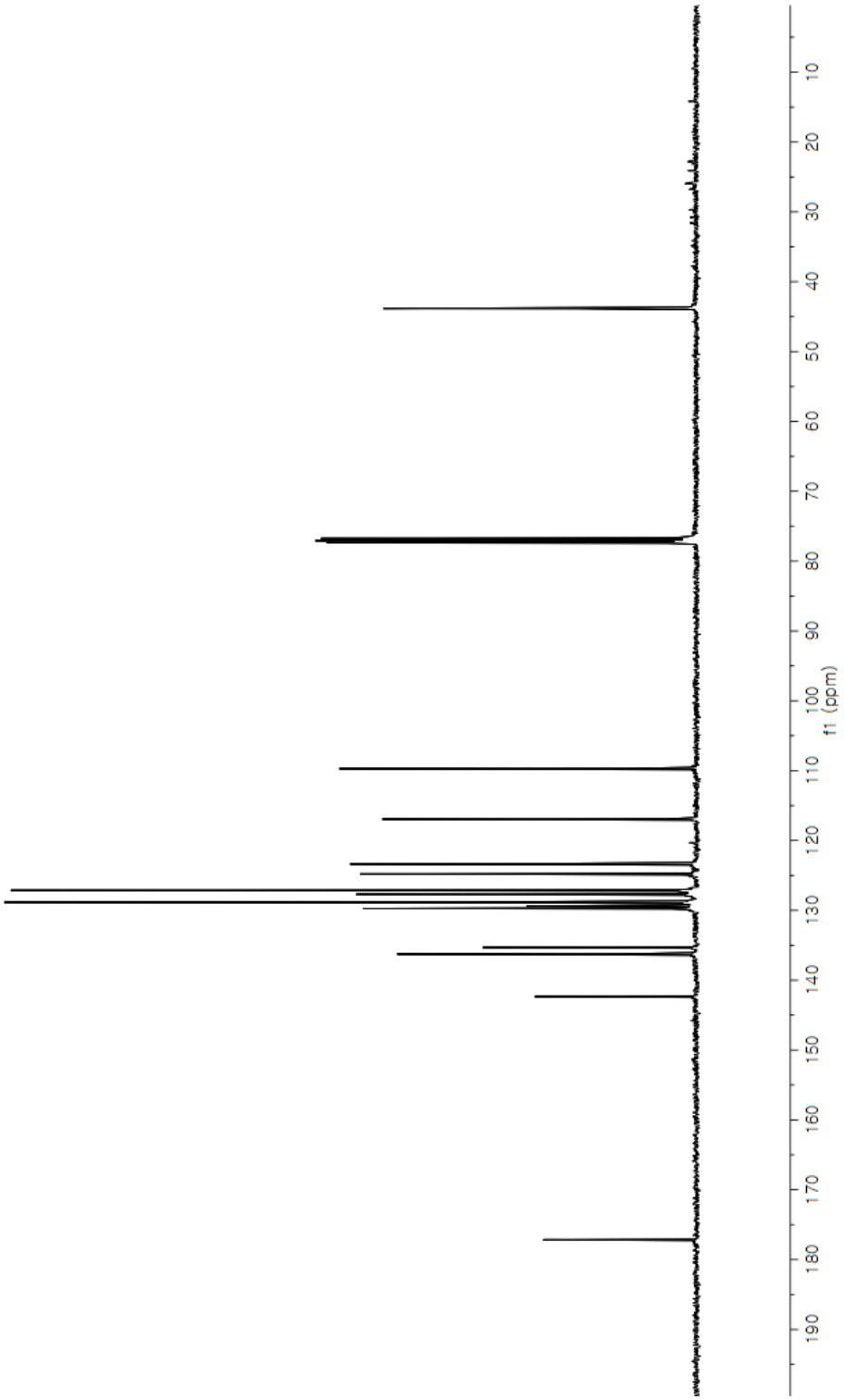
^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 142.5, 136.4, 135.4, 129.8, 129.5, 128.9, 127.8, 127.2, 124.9, 123.5, 117.0, 109.8, 77.3, 43.9.

LRMS (CI) Calcd. for $C_{17}H_{15}NO_2$ $[M+H]^+$: 266, Found: 266.

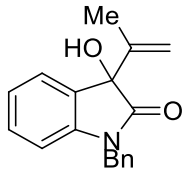
FTIR (neat): 3389, 1705, 1614.

MP: 128 °C.


1.01
1.04
1.03
1.03
1.03
1.00
1.02
1.07
6.89
1.05
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

1-Benzyl-3-hydroxy-3-(prop-1-en-2-yl)indolin-2-one (4.3h)



The reaction was conducted at 130 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 10% EtOAc/hexanes to 20% EtOAc/hexanes) provided the title compound (71.2 mg, 85%) as a yellow solid.

R_f: 0.20 (EtOAc:hexanes = 1:4)

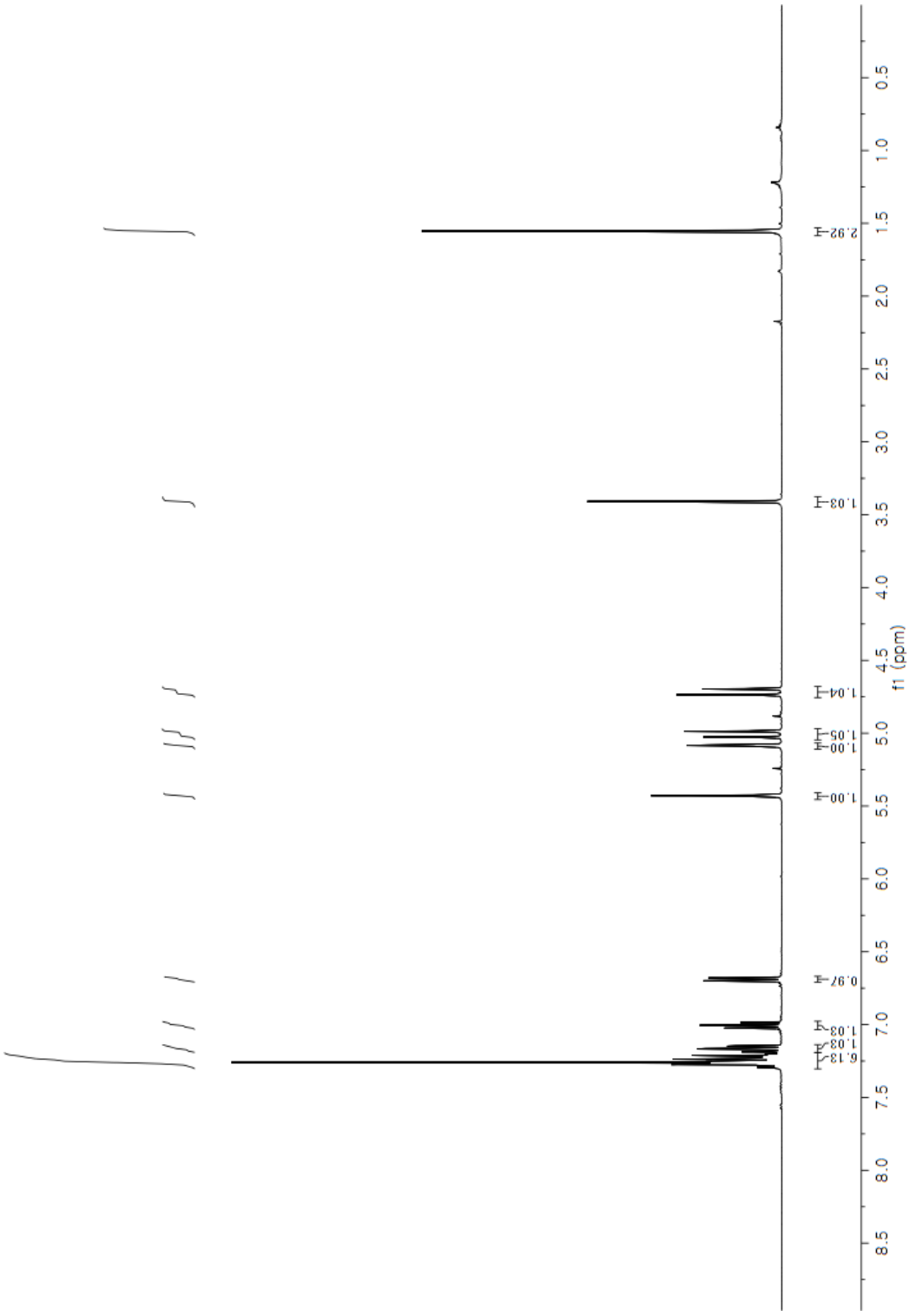
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.15 (m, 6H), 7.17 (ddd, *J* = 7.8 Hz, 7.8 Hz, 1.2 Hz, 1H), 7.00 (ddd, *J* = 7.6 Hz, 7.6 Hz, 1.0 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 5.430-5.426 (m, 1H), 5.09–5.08 (m, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 4.72 (d, *J* = 15.6 Hz, 1H), 3.41 (s, 1H), 1.55 (dd, *J* = 1.6 Hz, 0.8 Hz, 3H).

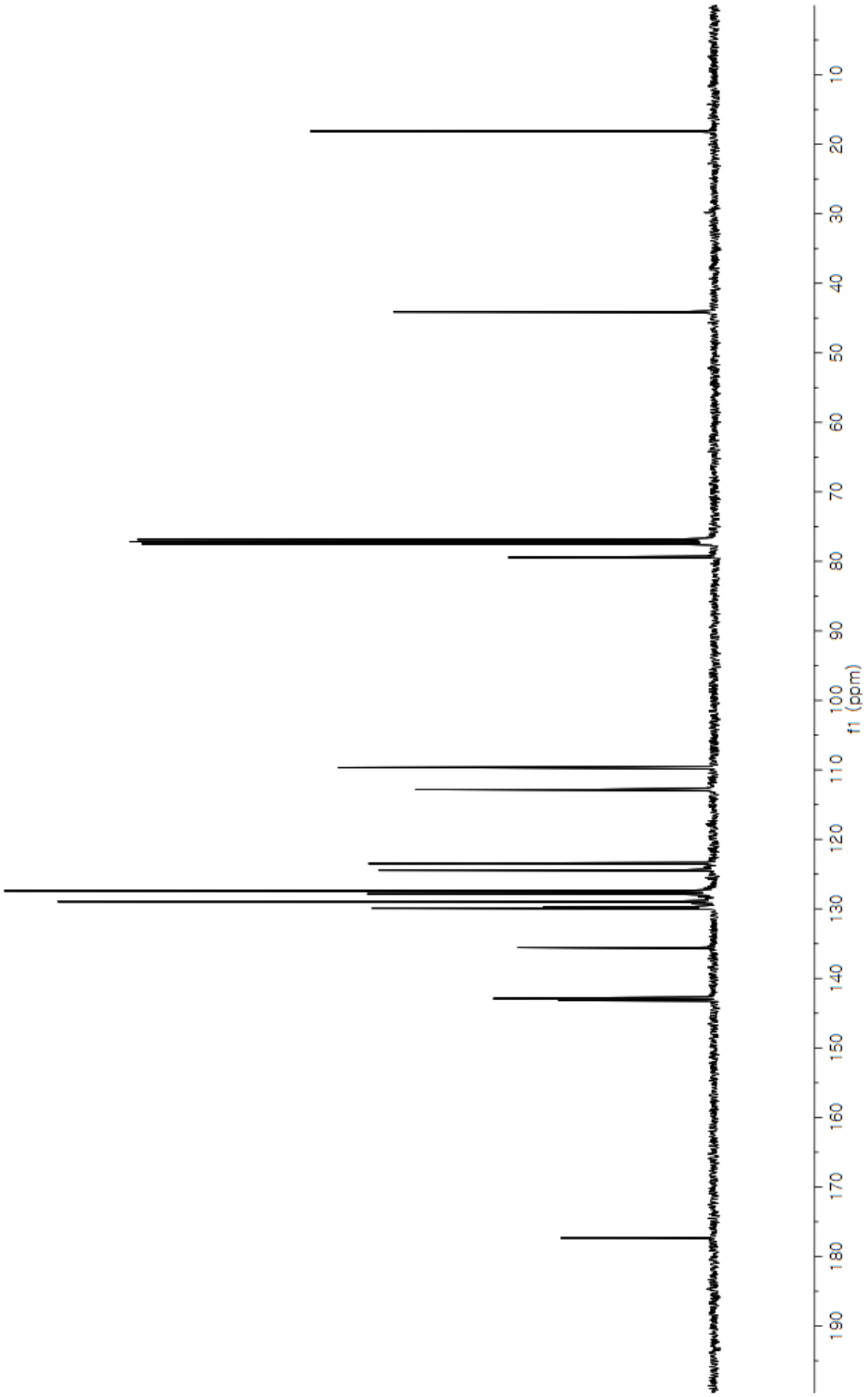
^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 143.2, 142.9, 135.6, 129.9, 129.7, 128.9, 127.8, 127.4, 124.4, 123.5, 112.8, 109.7, 79.4, 44.1, 18.1.

LRMS (CI) Calcd. for $C_{18}H_{17}NO_2$ $[M+H]^+$: 280, Found: 280.

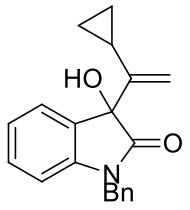
FTIR (neat): 3390, 1702, 1612.

MP: 134 °C.


2.92
1.03
1.04
1.05
1.00
1.00
0.97
1.03
1.03
6.13
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

1-Benzyl-3-(1-cyclopropylvinyl)-3-hydroxyindolin-2-one (4.3i)



Using 1-Cyclopropylvinyl 2,2,2-triphenylacetate (4.2c)

The reaction was conducted at 130 °C for a 48 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 10% EtOAc/hexanes to 20% EtOAc/hexanes) provided the title compound (77.9 mg, 85%) as a yellow solid.

R_f: 0.19 (EtOAc:hexanes = 1:4)

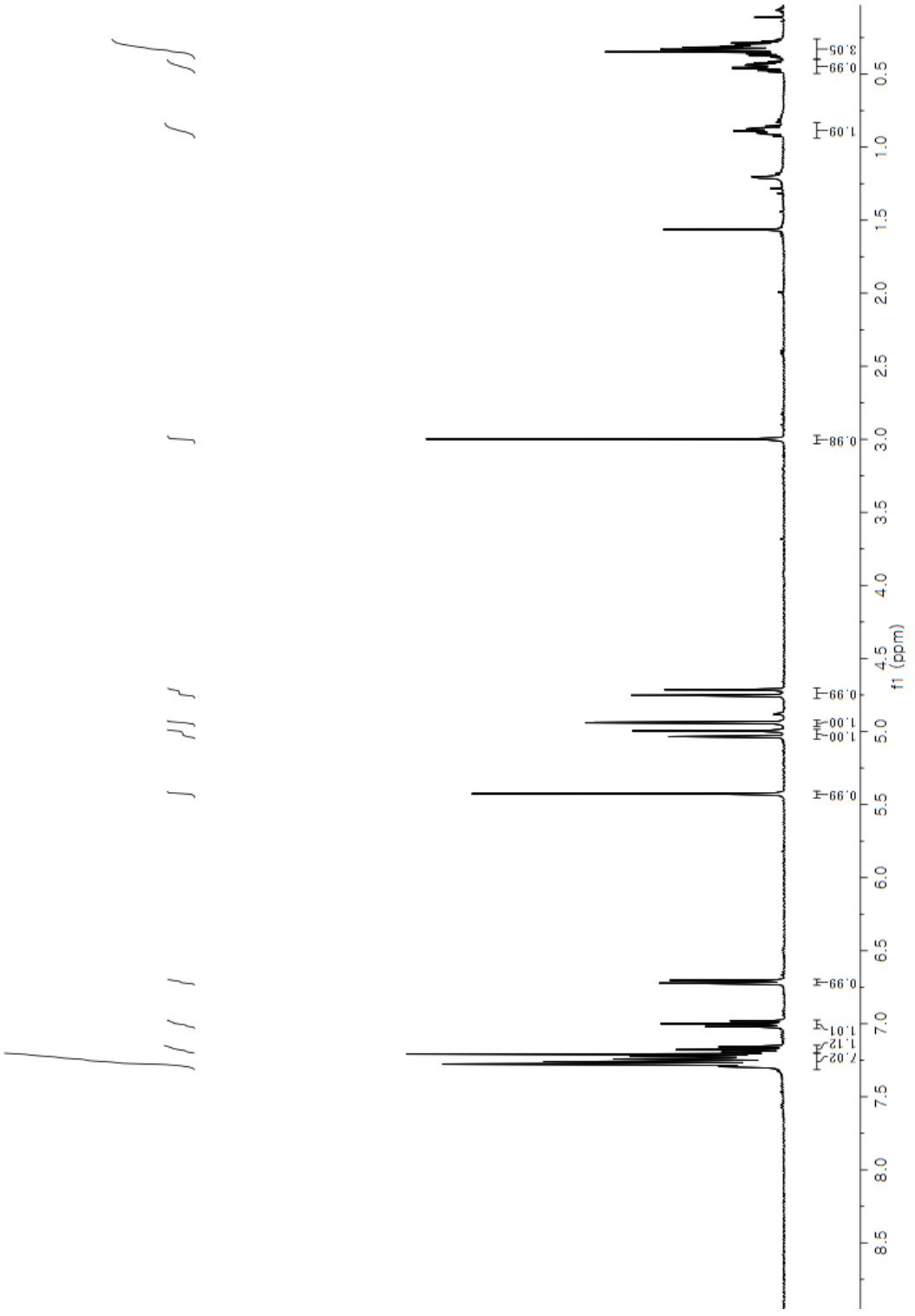
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.21 (m, 7H), 7.18 (ddd, *J* = 7.6 Hz, 7.6 Hz, 1.0 Hz, 1H), 7.00 (dd, *J* = 7.4 Hz, 7.4 Hz, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 5.43 (s, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 4.94 (s, 1H), 4.73 (d, *J* = 15.6 Hz, 1H), 3.00 (s, 1H), 0.92–0.83 (m, 1H), 0.48–0.41 (m, 1H), 0.39–0.26 (m, 3H).

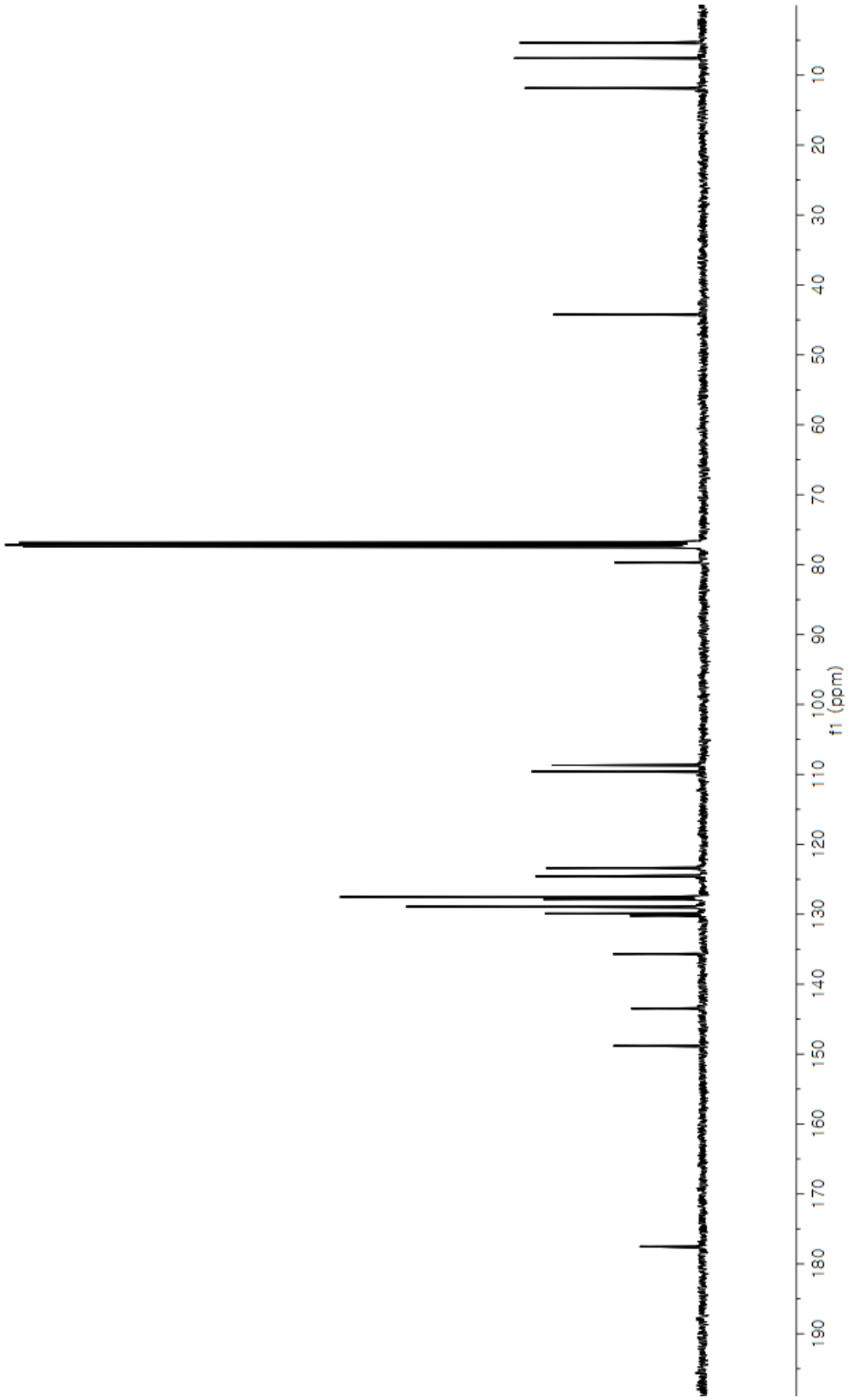
^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 148.8, 143.5, 135.7, 130.2, 129.9, 128.9, 127.9, 127.5, 124.6, 123.4, 109.6, 108.7, 79.7, 44.2, 11.9, 7.6, 5.4.

LRMS (ESI) Calcd. for $C_{20}H_{19}NO_2$ $[M+Na]^+$: 328, Found: 328.

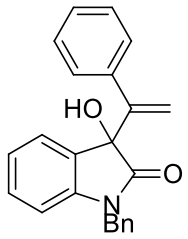
FTIR (neat): 3355, 3006, 1630.

MP: 142 °C.


3.05
0.99
1.09
0.98
0.99
1.00
1.00
0.99
0.99
1.01
1.12
2.02
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

1-Benzyl-3-hydroxy-3-(1-phenylvinyl)indolin-2-one (4.3j).



The reaction was conducted at 130 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 10% EtOAc/hexanes to 20% EtOAc/hexanes) provided the title compound (89.1 mg, 87%) as a white solid.

R_f: 0.16 (EtOAc:hexanes = 1:4).

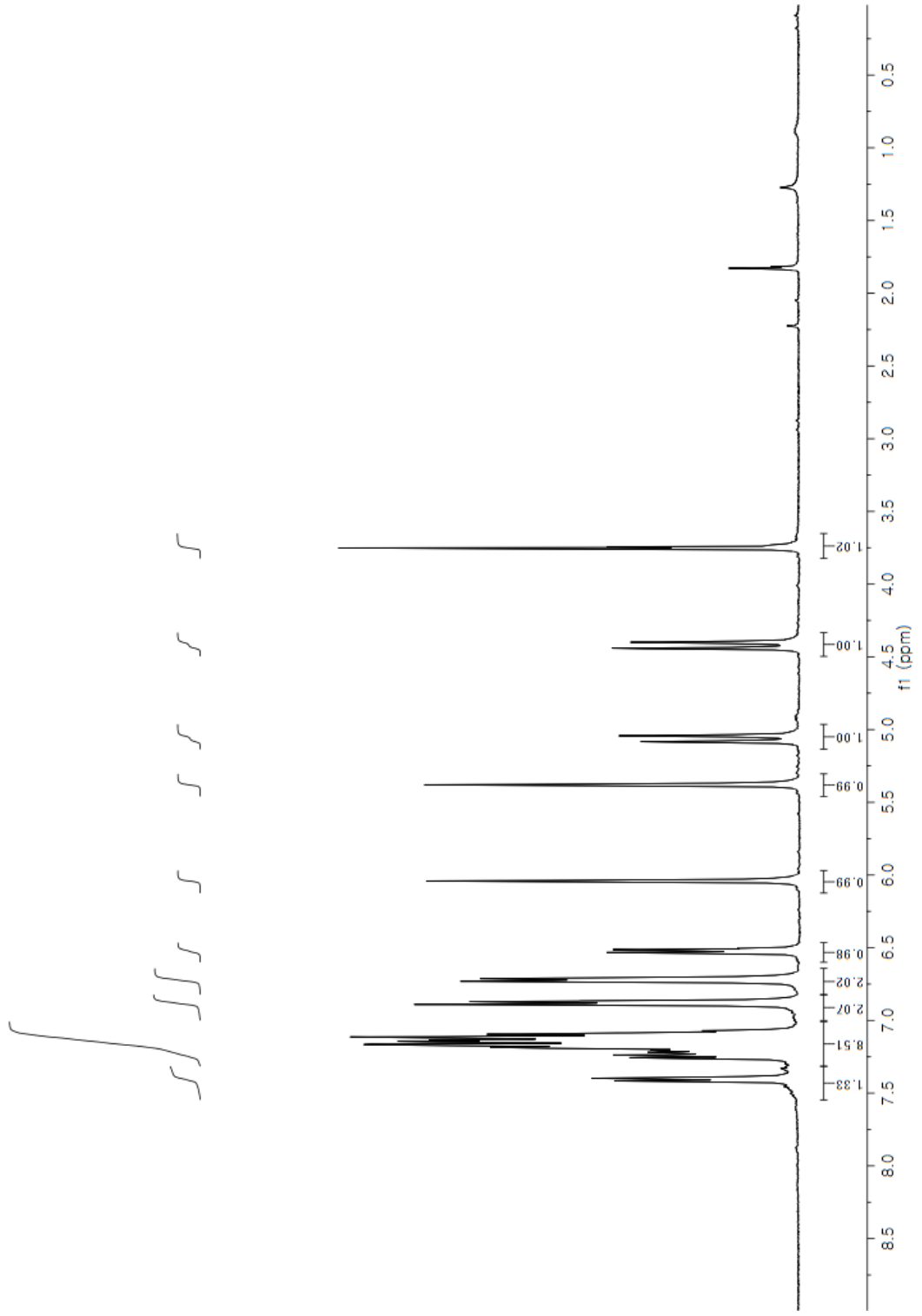
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.6 Hz, 1H), 7.26–7.07 (m, 8H), 6.89–6.86 (m, 2H), 6.72 (d, *J* = 7.6 Hz, 2H), 6.52 (d, *J* = 7.6 Hz, 1H), 6.04 (s, 1H), 5.38 (s, 1H), 5.06 (d, *J* = 16.0 Hz, 1H), 4.42 (d, *J* = 16.0 Hz, 1H), 3.75 (s, 1H).

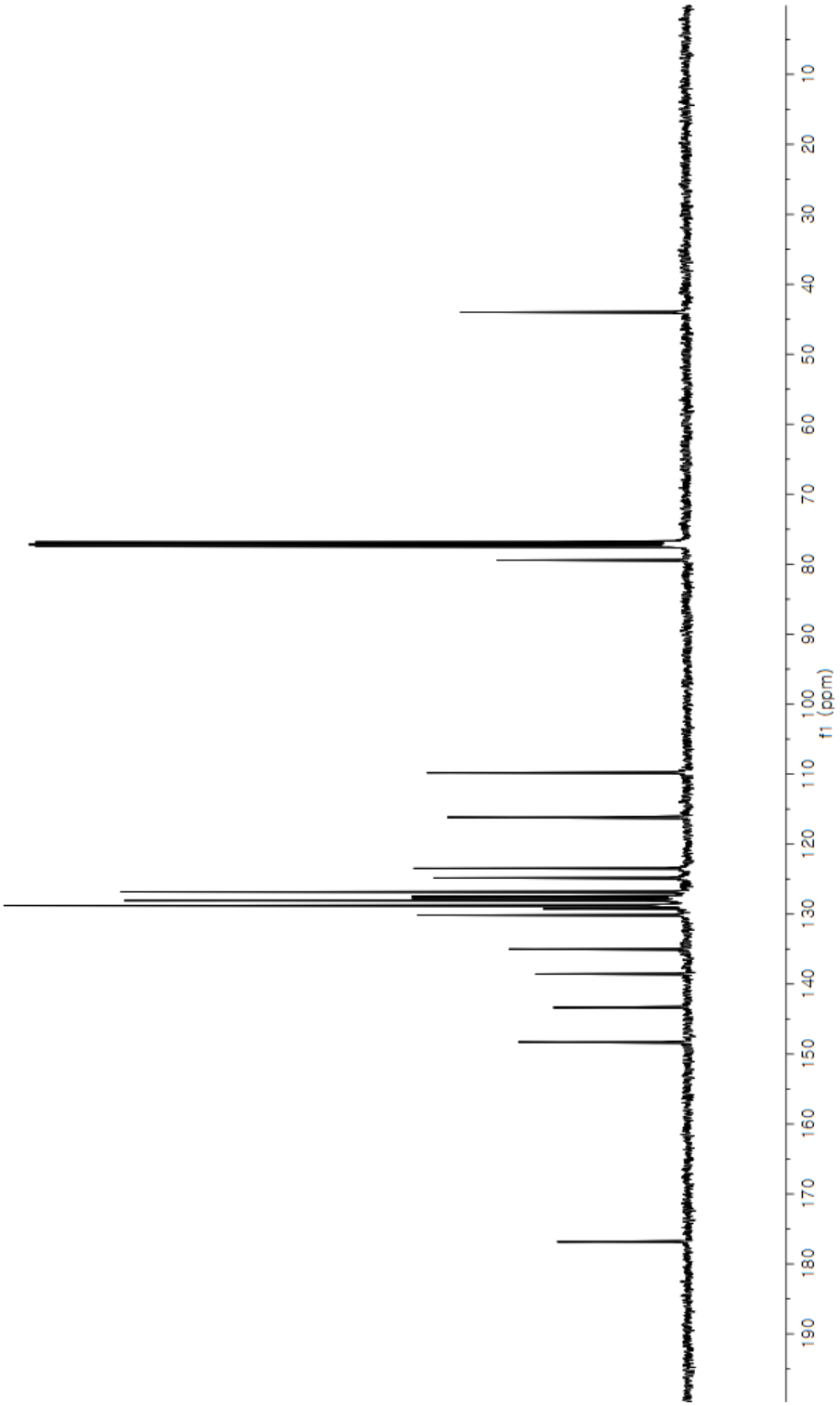
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 148.3, 143.4, 138.6, 135.0, 130.2, 128.80, 128.77, 128.0, 127.7, 127.5, 126.8, 123.5, 116.2, 109.8, 79.4, 44.0 (2 missing carbons).

LRMS (ESI) Calcd. for $C_{23}H_{19}NO_2$ $[M+Na]^+$: 364, Found: 364.

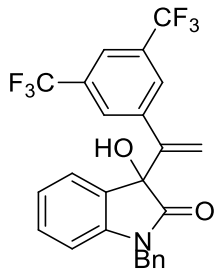
FTIR (neat): 3390, 1702, 1612.

MP: 150 °C.


1.02
1.00
1.00
0.99
0.99
0.98
2.02
2.07
8.51
1.33
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

1-Benzyl-3-(1-(3,5-bis(trifluoromethyl)phenyl)vinyl)-3-hydroxyindolin-2-one (4.3k)



The reaction was conducted at 130 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 10% EtOAc/hexanes to 20% EtOAc/hexanes) provided the title compound (134.6 mg, 94%) as a yellow solid.

R_f: 0.26 (EtOAc:hexanes = 1:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.36 (dd, *J* = 7.6 Hz, 0.8 Hz, 1H), 7.26–7.22 (m, 3H), 7.19–7.10 (m, 4H), 6.80 (d, *J* = 6.8 Hz, 2H), 6.64 (d, *J* = 7.6 Hz, 1H), 6.10 (s, 1H), 5.41 (s, 1H), 4.86 (d, *J* = 15.6 Hz, 1H), 4.48 (d, *J* = 15.6 Hz, 1H), 4.27 (s, 1H).

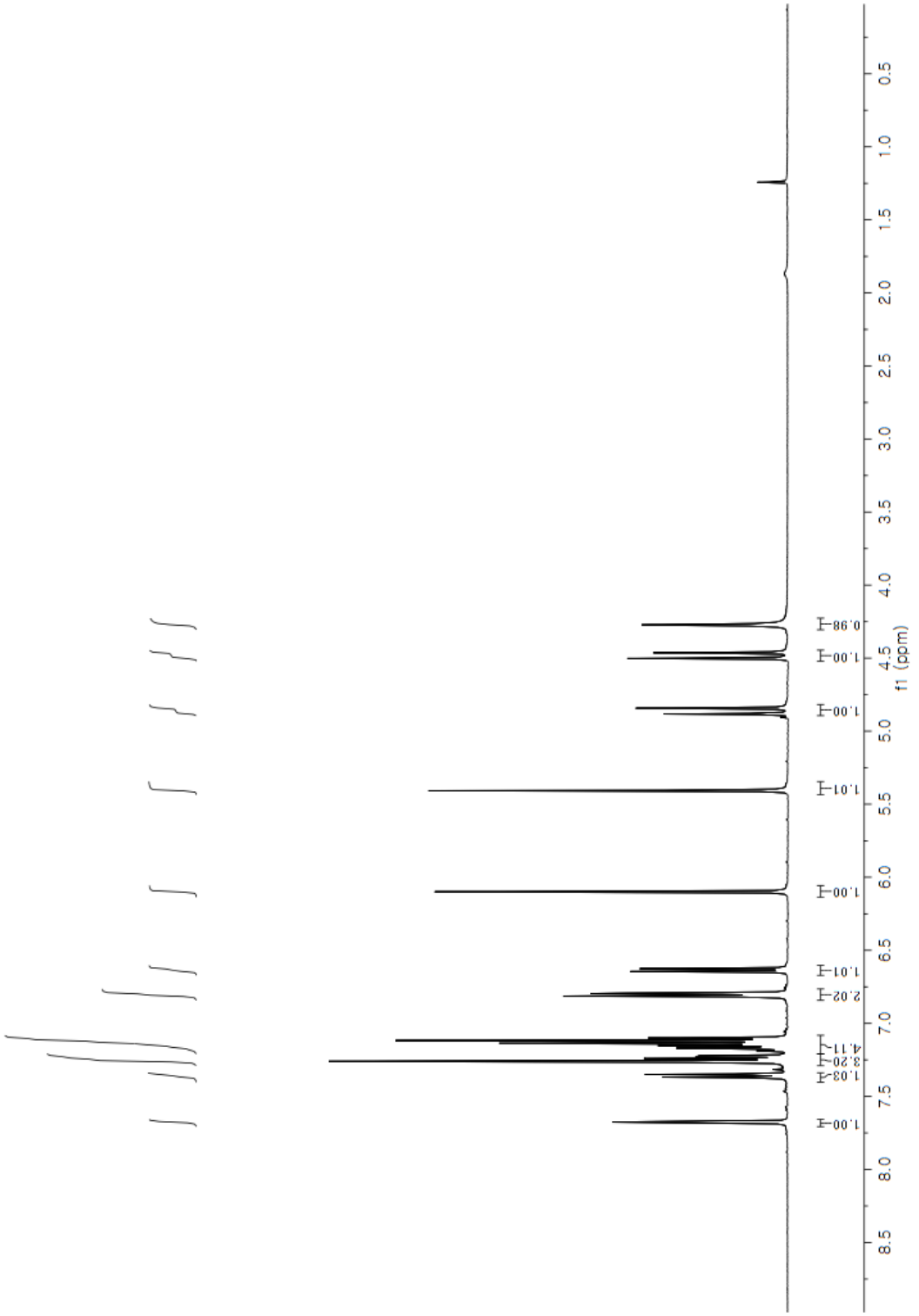
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.4, 146.2, 143.1, 140.6, 134.8, 131.2 (q, *J* = 33.0 Hz), 130.7, 129.0, 128.8, 128.4, 127.8, 126.9, 124.9, 124.0, 123.1 (q, *J* = 271.0 Hz,), 121.73, 121.66, 118.5, 110.1, 79.2, 77.5, 77.2, 76.8, 44.1

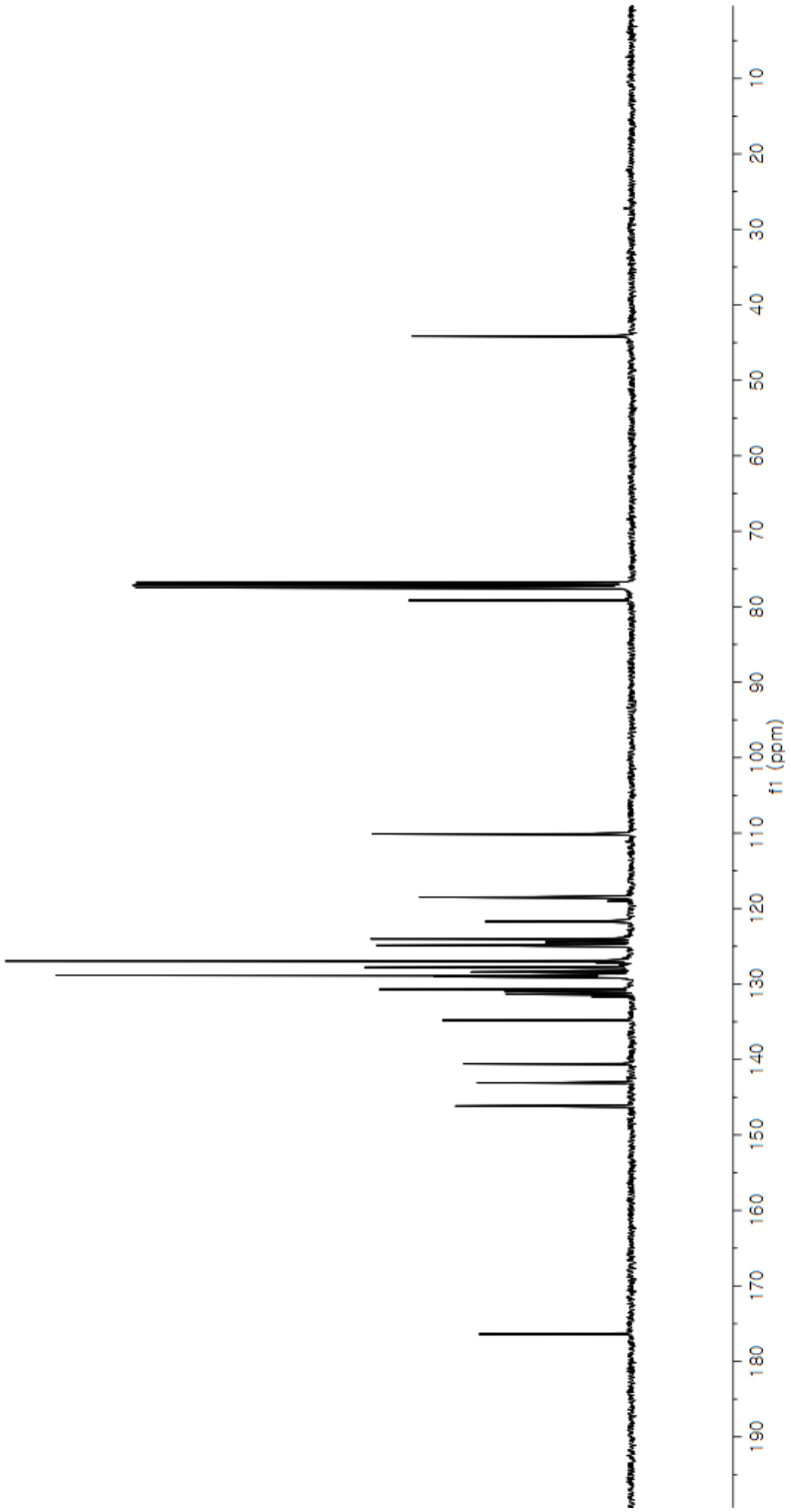
^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0.

LRMS (CI) Calcd. for $C_{25}H_{17}F_6NO_2$ $[M+H]^+$: 478, Found: 478.

FTIR (neat): 3394, 3308, 1692.

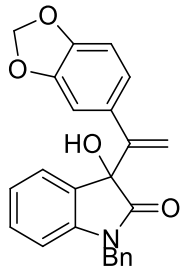
MP: 154 ^{o}C.


0.98
1.00
1.00
1.01
1.00
1.01
2.02
4.11
3.20
1.03
1.00
f1 (ppm)


10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)

10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
f1 (ppm)

3-(1-(Benzo[*d*][1,3]dioxol-5-yl)vinyl)-1-benzyl-3-hydroxyindolin-2-one (4.3l)



The reaction was conducted at 130 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 10% EtOAc/hexanes to 20% EtOAc/hexanes) provided the title compound (104.1 mg, 90%) as a white solid.

R_f: 0.11 (EtOAc:hexanes = 1:4).

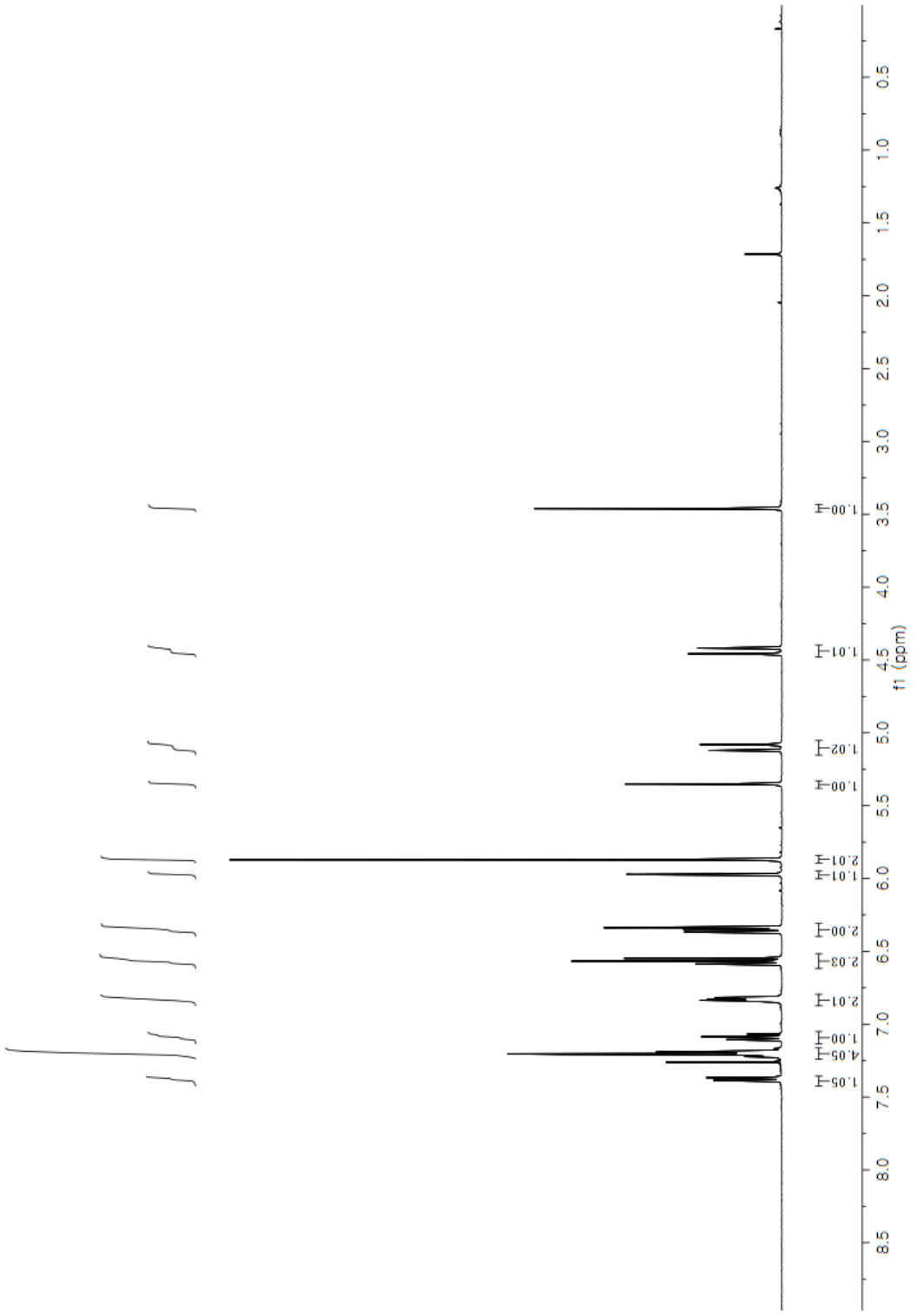
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 7.4 Hz, 1.4 Hz, 1H), 7.23–7.18 (m, 4H), 7.09 (ddd, *J* = 7.6 Hz, 7.6 Hz, 0.7 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.82 (d, *J* = 4.0 Hz, 1H), 6.57 (dd, *J* = 7.8 Hz, 7.8 Hz, 2H), 6.37–6.33 (m, 2H), 5.97 (d, *J* = 0.8 Hz, 1H), 5.87 (s, 2H), 5.35 (d, *J* = 0.8 Hz, 1H), 5.10 (d, *J* = 16.0 Hz, 1H), 4.44 (d, *J* = 16.0 Hz, 1H), 3.46 (s, 1H).

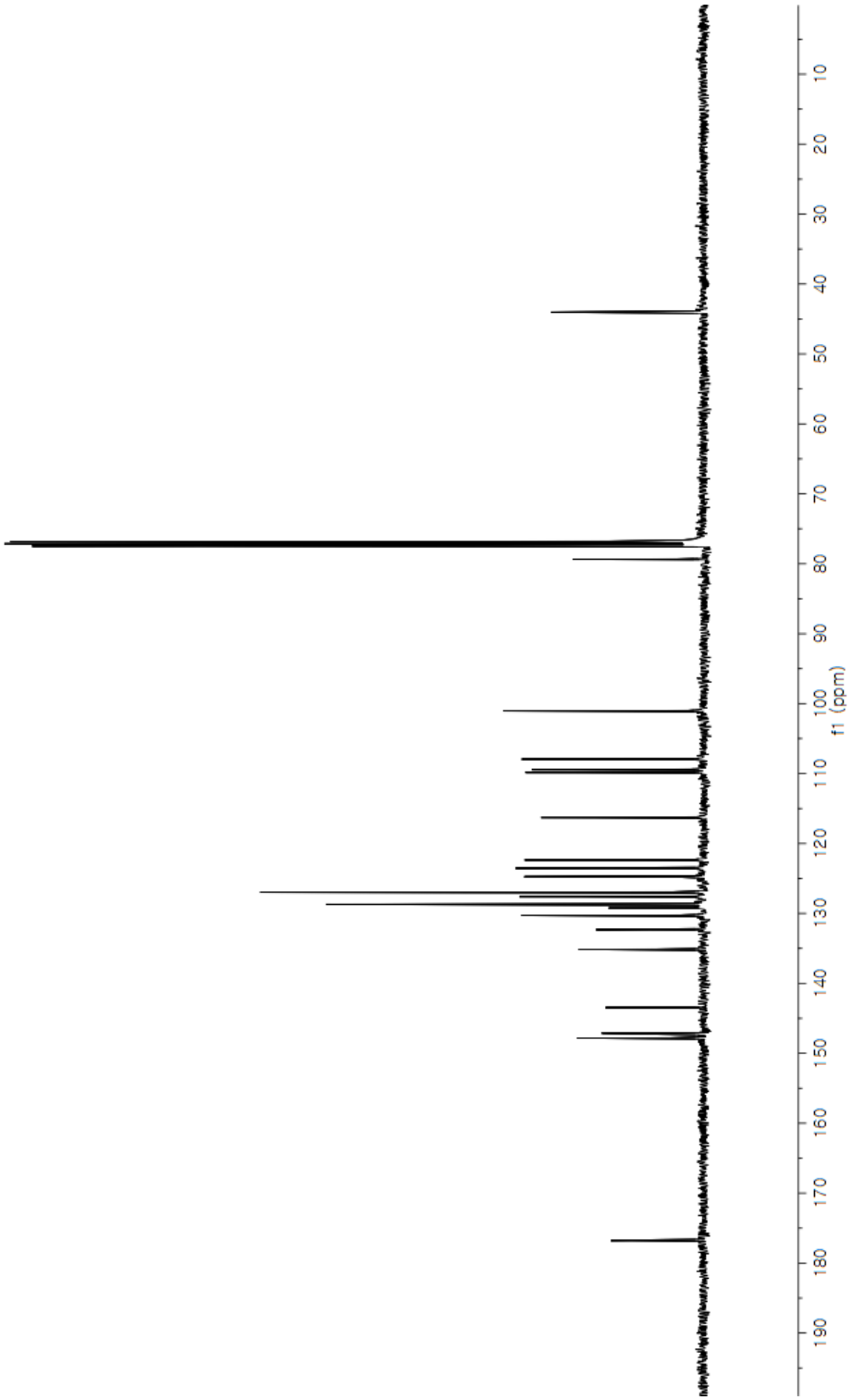
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 147.8, 147.2, 147.1, 143.5, 135.1, 132.3, 130.3, 129.2, 128.7, 127.6, 127.0, 124.8, 123.5, 122.4, 116.3, 109.8, 109.4, 108.0, 101.0, 79.4, 44.0.

LRMS (CI) Calcd. for $C_{24}H_{19}NO_4$ $[M+H]^+$: 386, Found: 386.

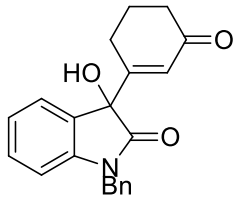
FTIR (neat): 3383, 3057, 1703.

MP: 152 ^{o}C.


1.00
1.01
1.02
1.00
2.01
1.01
2.00
2.03
2.01
1.00
4.05
1.05
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)



1-Benzyl-3-hydroxy-3-(1-(3-oxocyclohex-1-en-1-yl)vinyl)indolin-2-one (4.3m)



The reaction was conducted at 130 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 10% EtOAc/hexanes to 30% EtOAc/hexanes) provided the title compound (73.0 mg, 73%) as a yellow solid.

R_f: 0.07 (EtOAc:hexanes = 1:4).

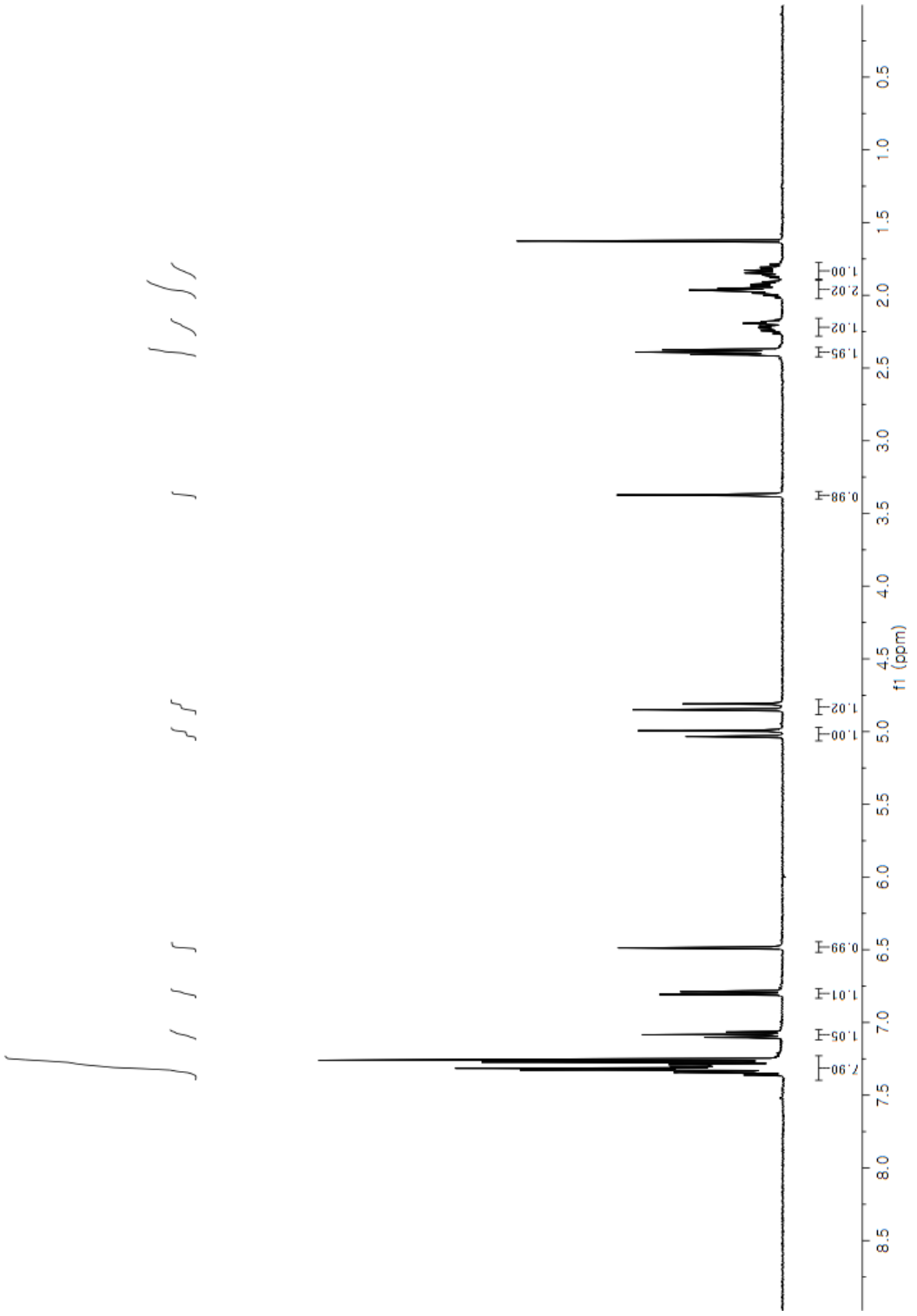
^{1}H NMR (400 MHz, $CDCl_3$): 7.40–7.23 (m, 7H), 7.12–7.05 (m, 1H), 6.83–6.77 (m, 1H), 6.49 (s, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.83 (d, J = 15.6 Hz, 1H), 3.37 (s, 1H), 2.42–2.36 (m, 2H), 2.28–2.16 (m, 1H), 2.02–1.90 (m, 2H), 1.89–1.78 (m, 1H).

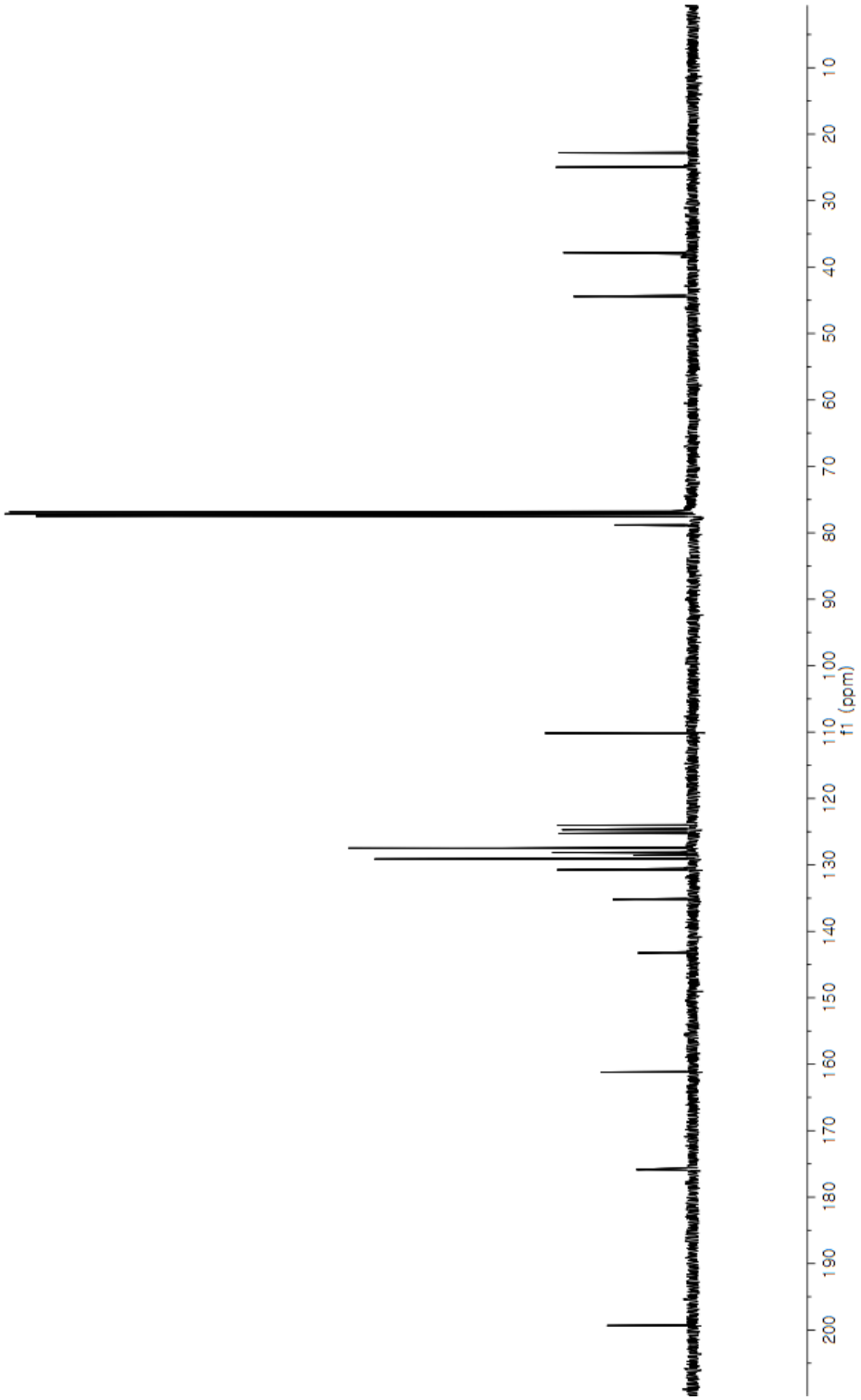
^{13}C NMR (100 MHz, $CDCl_3$): δ 199.4, 175.9, 161.2, 143.2, 135.2, 130.7, 129.1, 128.5, 128.1, 127.5, 125.3, 124.7, 124.0, 110.2, 78.8, 44.4, 37.8, 25.0, 22.8.

LRMS (ESI) Calcd. for $C_{21}H_{19}NO_3$ $[M+Na]^+$: 356, Found: 356.

FTIR (neat): 3337, 3059, 1714.

MP: 190 °C.


7.90
1.05
1.01
0.99
1.00
1.02
0.98
1.95
1.02
2.02
1.00
f1 (ppm)


10
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110
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130
140
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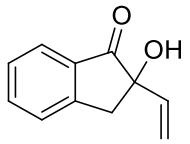
170
180
190
200
f1 (ppm)

2-hydroxy-2-vinyl-2,3-dihydro-1*H*-inden-1-one (4.3n).



The reaction was conducted with 500 mol% of vinyl pivalate at 130 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 5% EtOAc/hexanes to 10% EtOAc/hexanes) provided the title compound (35.0 mg, 67%) as a pale yellow oil.

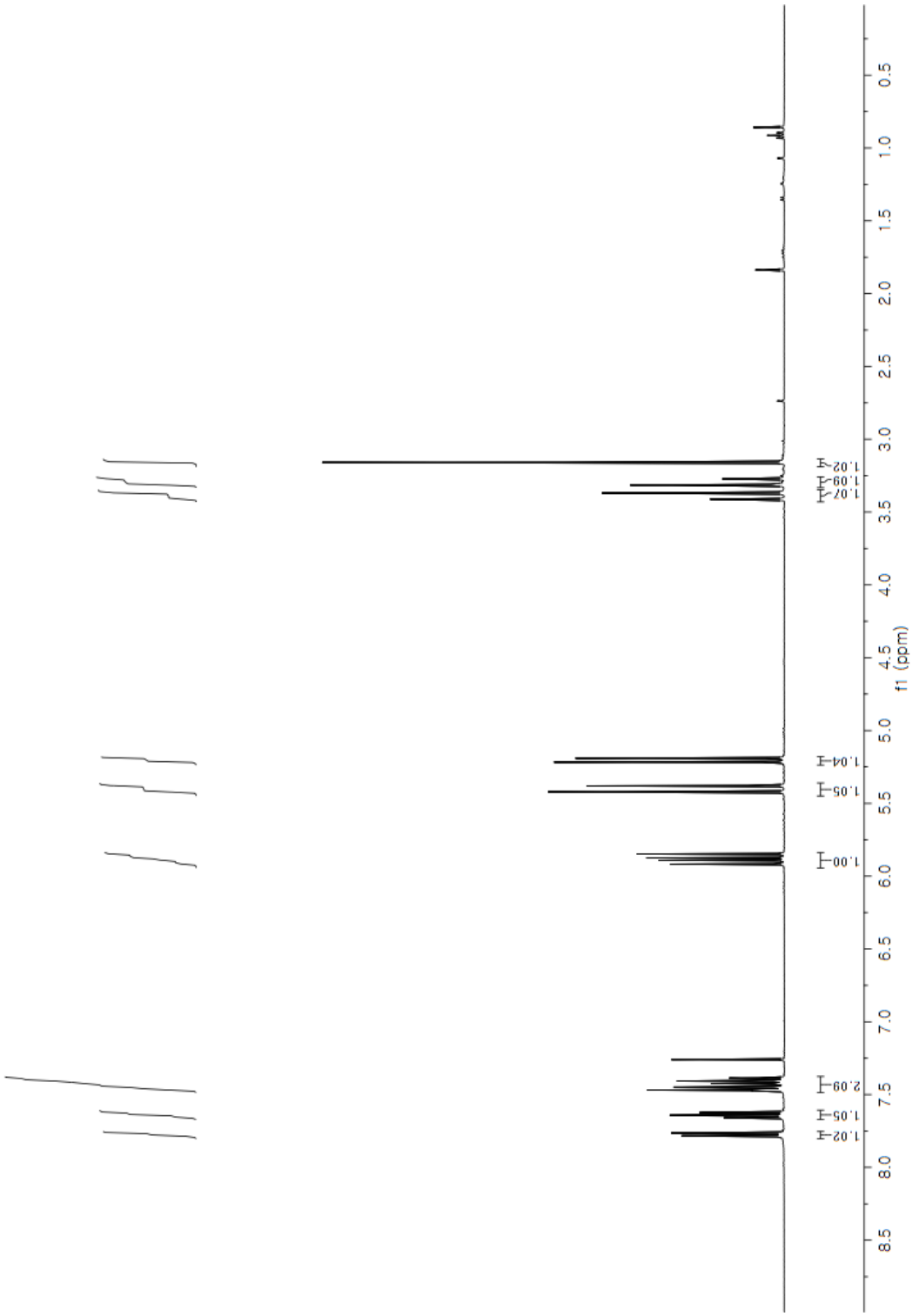
R_f: 0.22 (EtOAc:hexanes = 1:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 1H), 7.62 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H), 7.45–7.37 (m, 2H), 5.88 (dd, *J* = 17.2 Hz, 10.8 Hz, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.8 Hz, 1H), 3.40–3.36 (m, 2H), 3.29 (d, *J* = 16.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 205.7, 151.1, 138.1, 136.1, 133.9, 128.1, 126.8, 125.1, 115.2, 81.0, 41.3.

LRMS (ESI) Calcd. for $C_{11}H_{10}O_2$ $[M+Na]^+$: 197, Found: 197.

FTIR (neat): 3430, 1710.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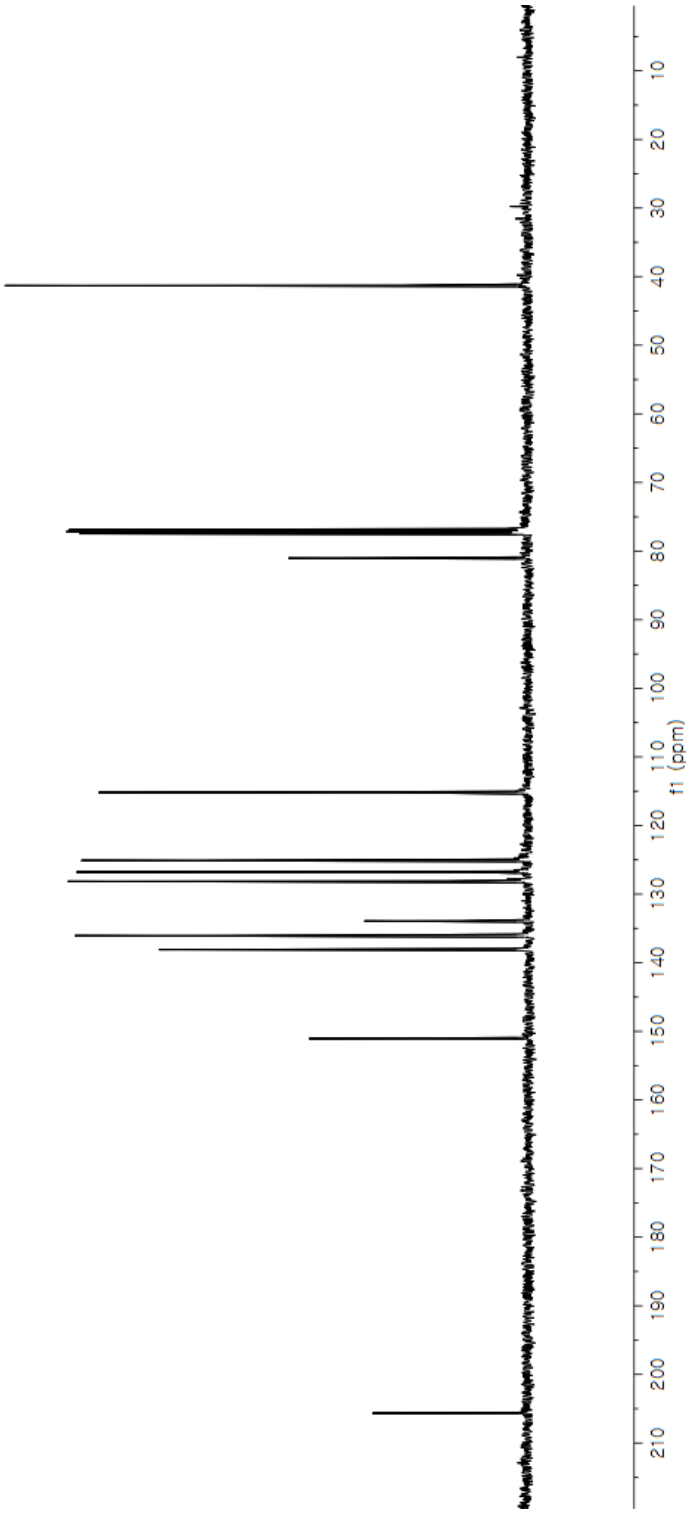
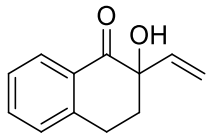
1.07
1.04
1.05
1.00
2.09
1.05
1.02
f1 (ppm)


f1 (ppm)

2-Hydroxy-2-vinyl-3,4-dihydronaphthalen-1(2*H*)-one (4.3o)



The reaction was conducted with 500 mol% of vinyl pivalate at 140 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 1% EtOAc/hexanes to 2% EtOAc/hexanes) provided the title compound (39.5 mg, 70%) as a pale yellow oil.

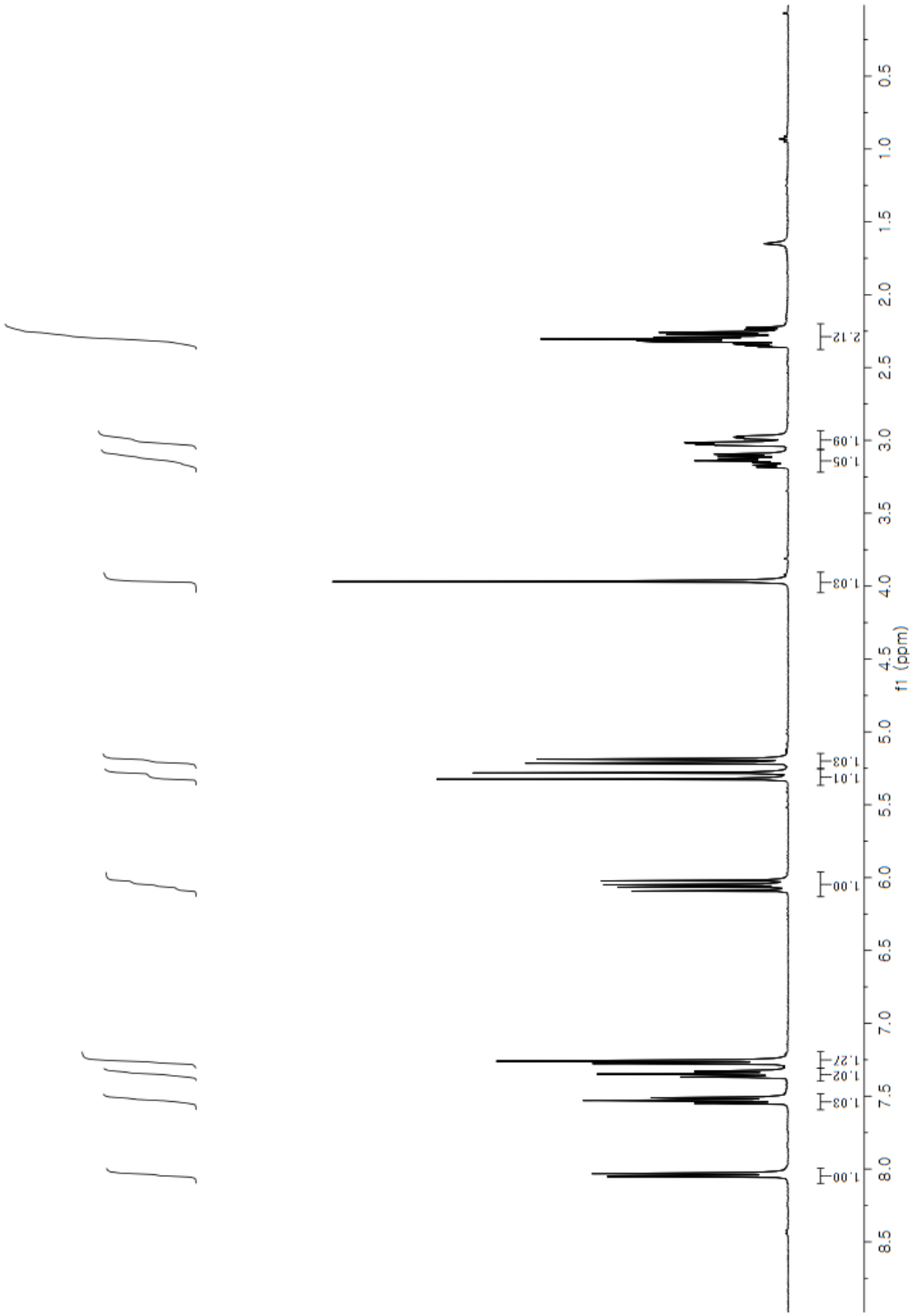
R_f: 0.48 (EtOAc:hexanes = 1:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.0 Hz, 1H), 7.53 (ddd, *J* = 7.6 Hz, 7.6 Hz, 1.5 Hz, 1H), 7.37–7.33 (m, 1H), 7.27 (dd, *J* = 7.0 Hz, 0.6 Hz, 1H), 6.06 (ddd, *J* = 17.6 Hz, 10.8 Hz, 1.1 Hz, 1H), 5.30 (ddd, *J* = 17.2 Hz, 1.0 Hz, 1.0 Hz, 1H), 5.20 (dd, *J* = 10.8 Hz, 0.8 Hz, 1H), 3.97 (s, 1H), 3.14 (ddd, *J* = 12.6 Hz, 17.6 Hz, 1.3 Hz, 1H), 3.00 (ddd, *J* = 17.4 Hz, 5.0 Hz, 1.8 Hz, 1H), 2.36–2.33 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 144.0, 136.8, 134.3, 130.8, 129.2, 128.0, 127.1, 117.2, 76.9, 35.6, 26.6.

LRMS (CI) Calcd. for $C_{12}H_{12}O_2$ $[M+H]^+$: 189, Found: 189.

FTIR (neat): 3476, 1684.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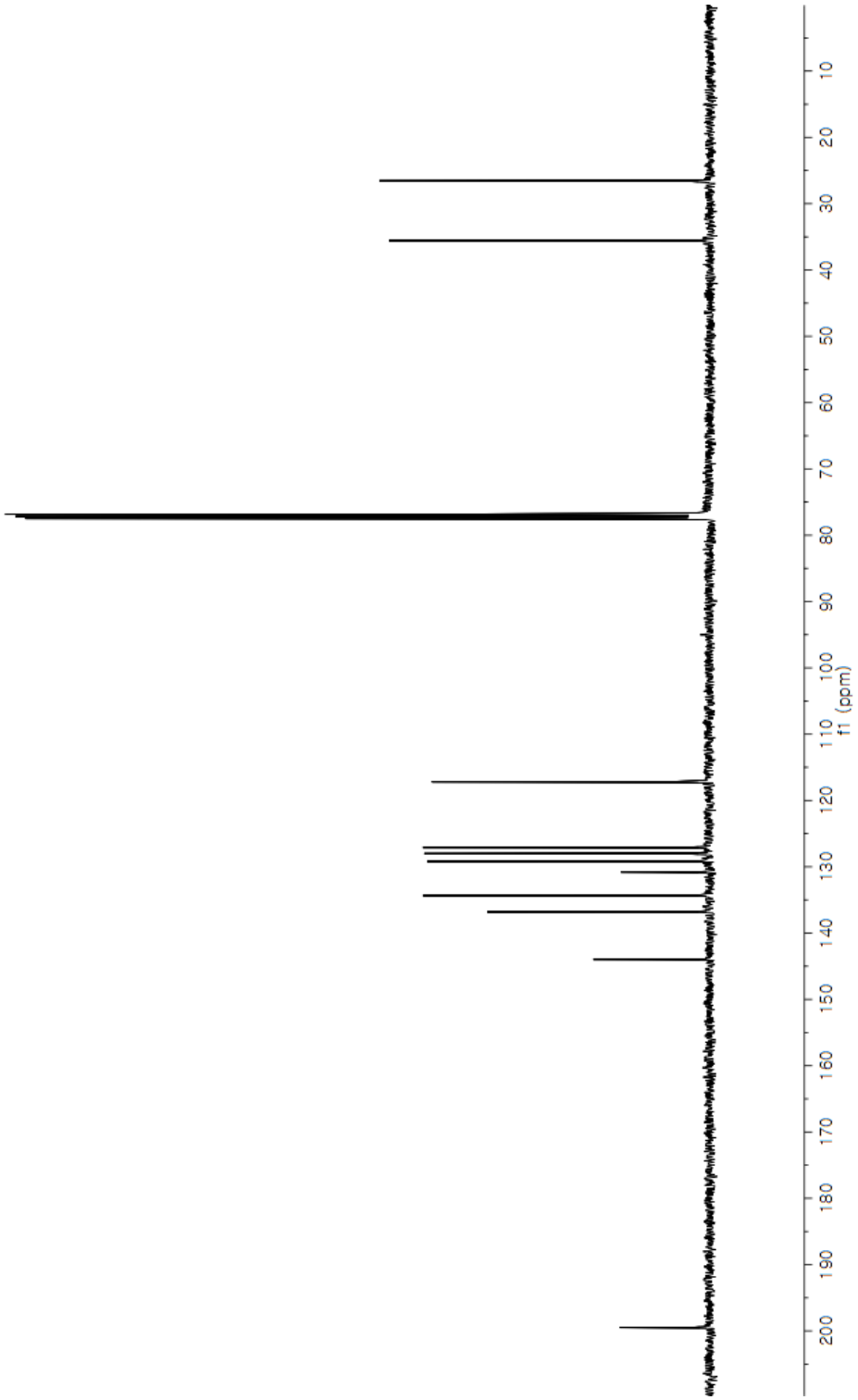
1.03
1.03
1.01
1.00
1.27
1.02
1.03
1.00
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


10
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70
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90
100
110
120
130
140
150
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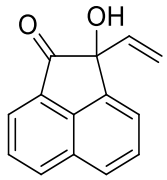
170
180
190
200
f1 (ppm)

2-Hydroxy-2-vinylacenaphthylen-1(2*H*)-one (4.3p)



The reaction was conducted with 500 mol% of vinyl pivalate at 150 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 5% EtOAc/hexanes to 10% EtOAc/hexanes) provided the title compound (37.9 mg, 60%) as a white solid.

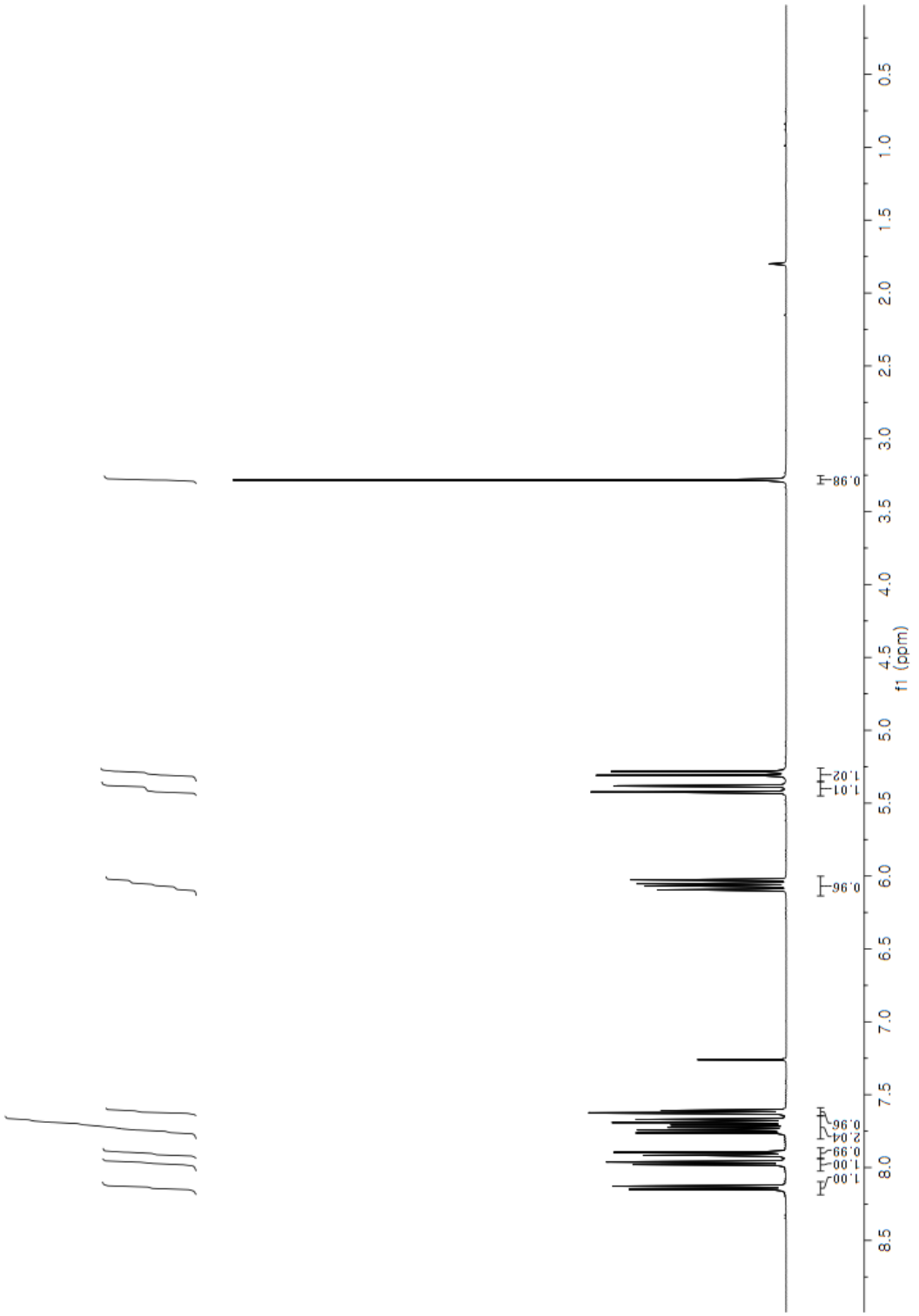
R_f: 0.22 (EtOAc:hexanes = 1:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 6.7 Hz, 1H), 7.92 (dd, *J* = 8.3 Hz, 0.6 Hz, 1H), 7.79–7.67 (m, 2H), 7.65–7.61 (m, 1H), 6.06 (dd, *J* = 17.2 Hz, 10.6 Hz, 1H), 5.42 (dd, *J* = 17.2 Hz, 0.8 Hz, 1H), 5.31 (dd, *J* = 10.6 Hz, 0.7 Hz, 1H), 3.09 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.5, 141.7, 138.8, 136.7, 132.3, 131.0, 130.6, 129.0, 128.6, 125.7, 122.8, 121.5, 116.7, 81.3.

LRMS (ESI) Calcd. for $C_{14}H_{10}O_2$ $[M+Na]^+$: 233, Found: 233.

FTIR (neat): 3386, 1706.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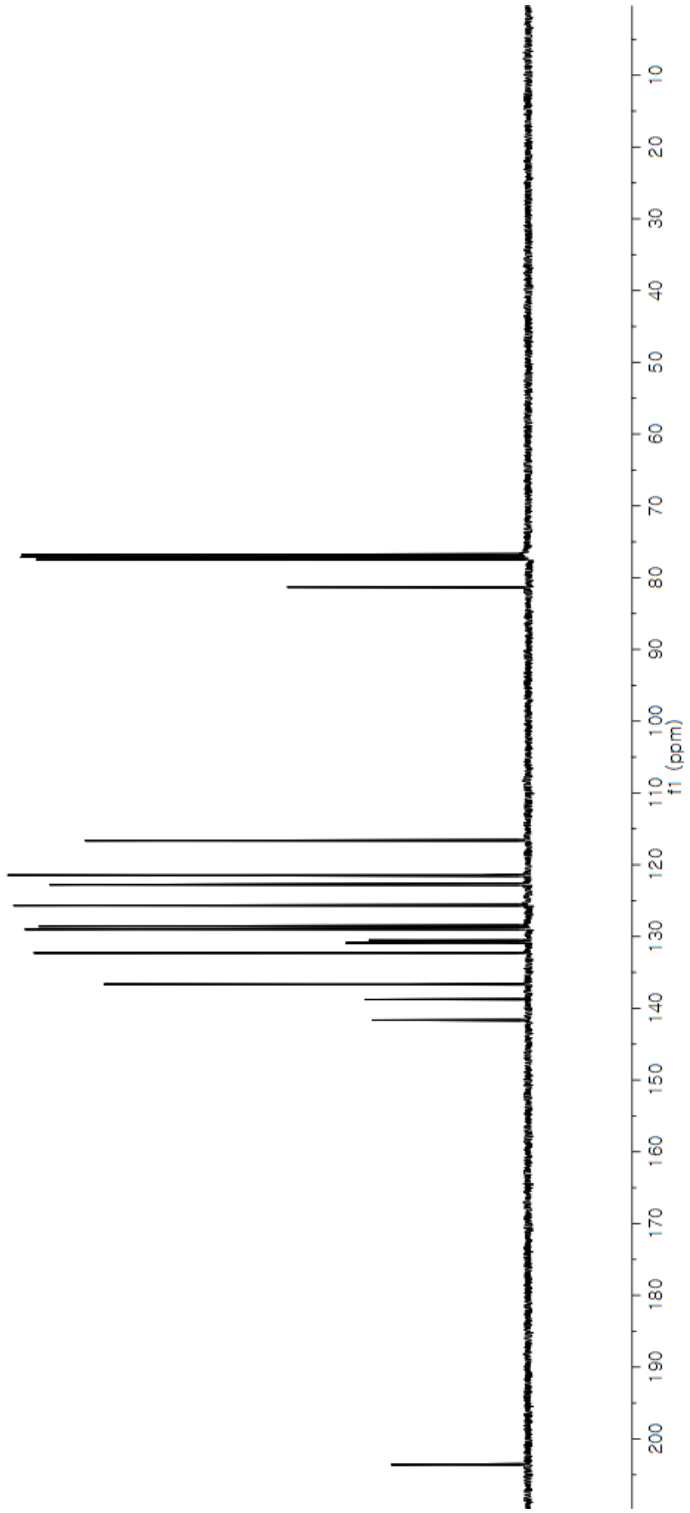
1.01
0.96
0.96
2.04
0.99
1.00
1.00
f1 (ppm)


10
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70
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100
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130
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150
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170
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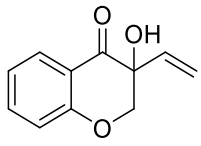
190
200
f1 (ppm)

3-Hydroxy-2,2-dimethyl-3-vinylchroman-4-one (4.3q)



The reaction was conducted with 500 mol% of vinyl pivalate at 140 °C for a 48 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 10% EtOAc/hexanes to 20% EtOAc/hexanes) provided the title compound (50.2 mg, 88%) as a colorless oil.

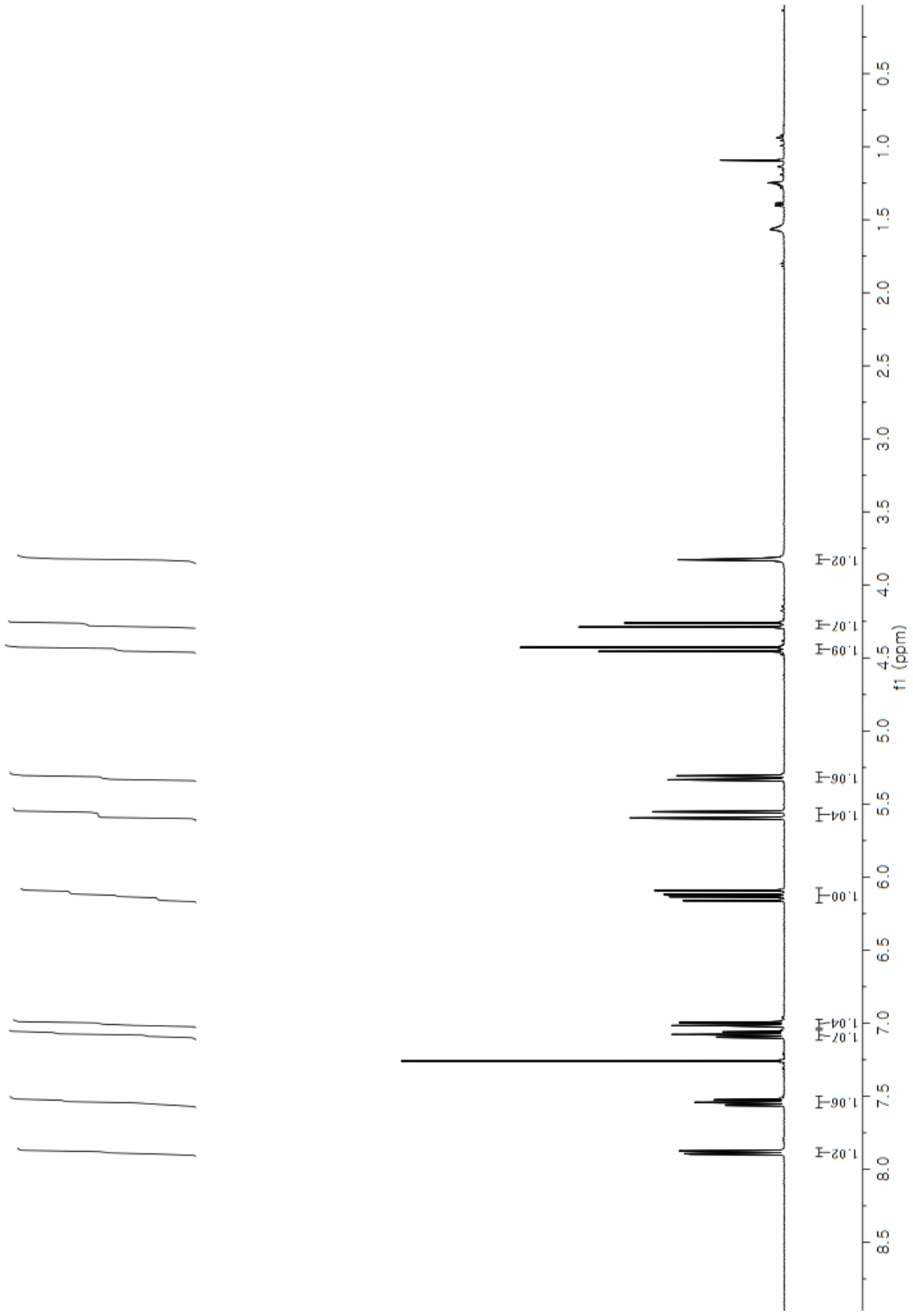
R_f: 0.45 (EtOAc:hexanes = 1:4).

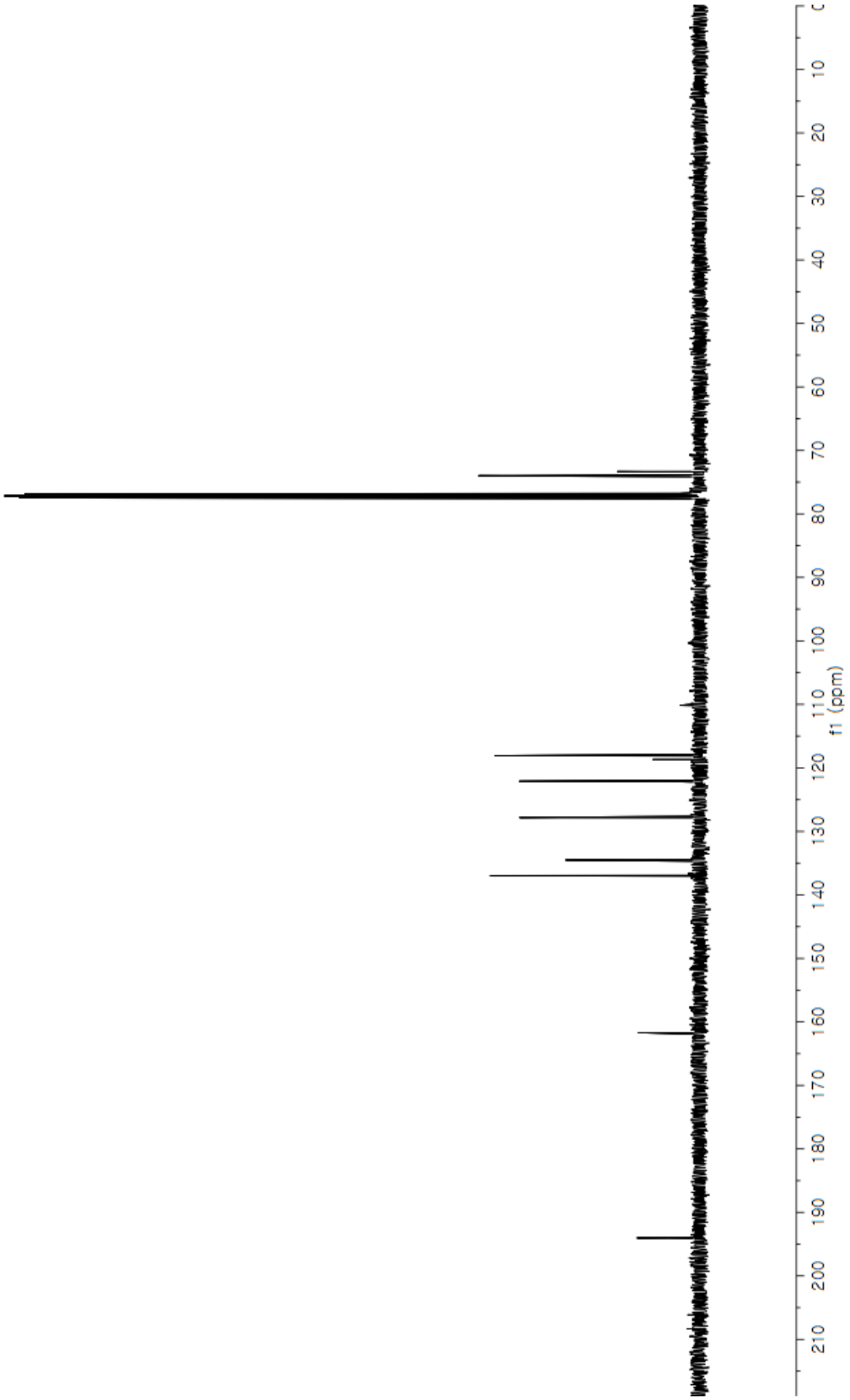
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.85 (m, 1H), 7.54 (ddd, *J* = 8.4 Hz, 7.2 Hz, 1.8 Hz, 1H), 7.08 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 7.03–6.97 (m, 1H), 6.13 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.57 (dd, *J* = 17.2 Hz, 0.9 Hz, 1H), 5.35–5.28 (m, 1H), 4.44 (d, *J* = 11.0 Hz, 1H), 4.30–4.24 (m, 1H), 3.83 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 161.7, 137.0, 134.5, 127.8, 122.1, 118.7, 118.2, 118.1, 74.0, 73.3.

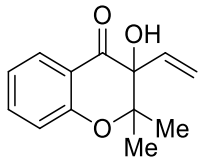
LRMS (ESI) Calcd. for $C_{11}H_{10}O_3$ $[M+Na]^+$: 213, Found: 213.

FTIR (neat): 3454, 2872, 1692.


1.02
1.07
1.09
1.06
1.04
1.00
1.04
1.07
1.06
1.02
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


f1 (ppm)

3-Hydroxy-2,2-dimethyl-3-vinylchroman-4-one (4.3r)



The reaction was conducted with 500 mol% of vinyl pivalate at 140 °C for a 40 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 1% EtOAc/hexanes to 2% EtOAc/hexanes) provided the title compound (57.0 mg, 87%) as a pale yellow oil.

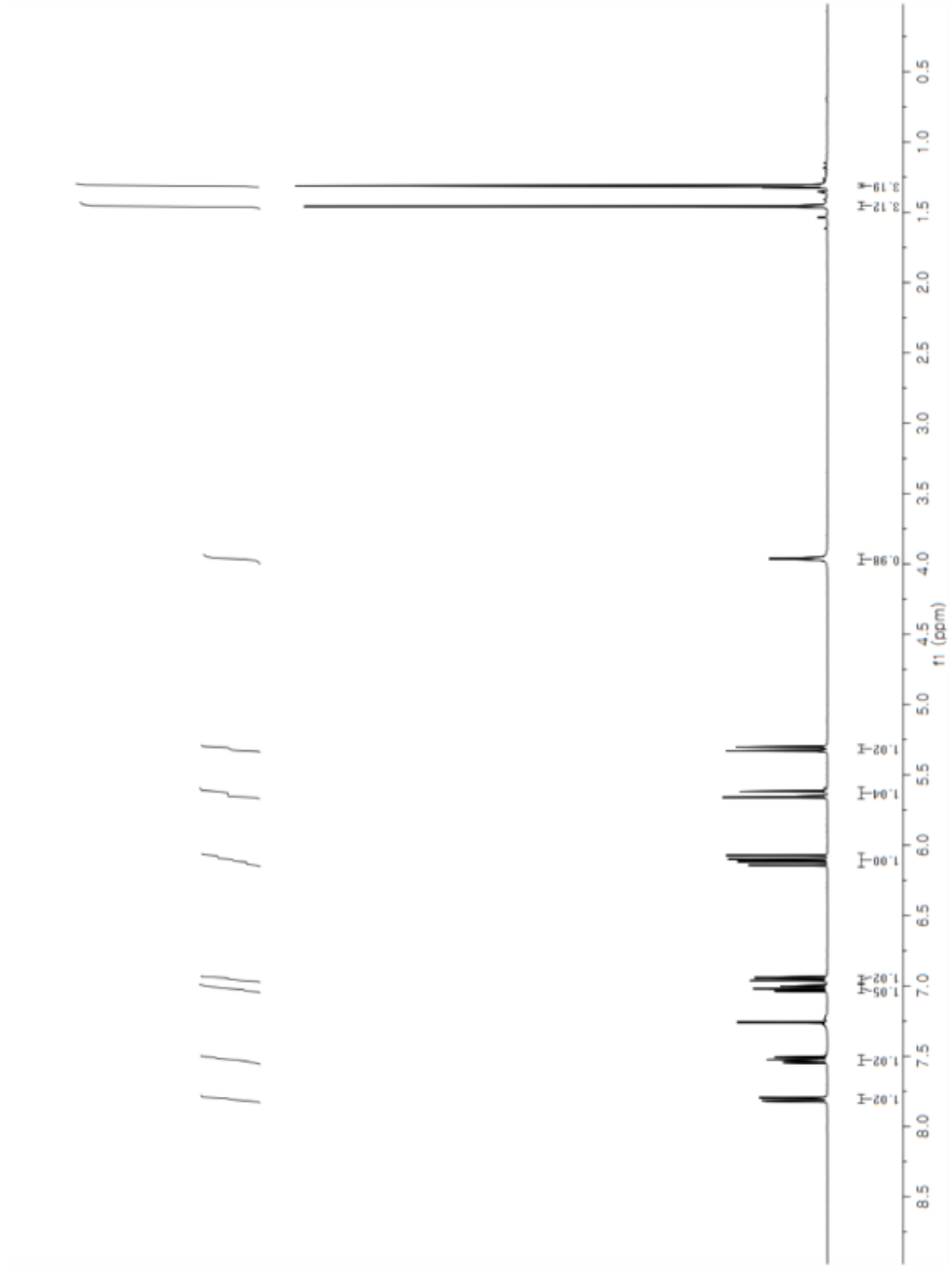
R_f: 0.72 (EtOAc:hexanes = 1:4).

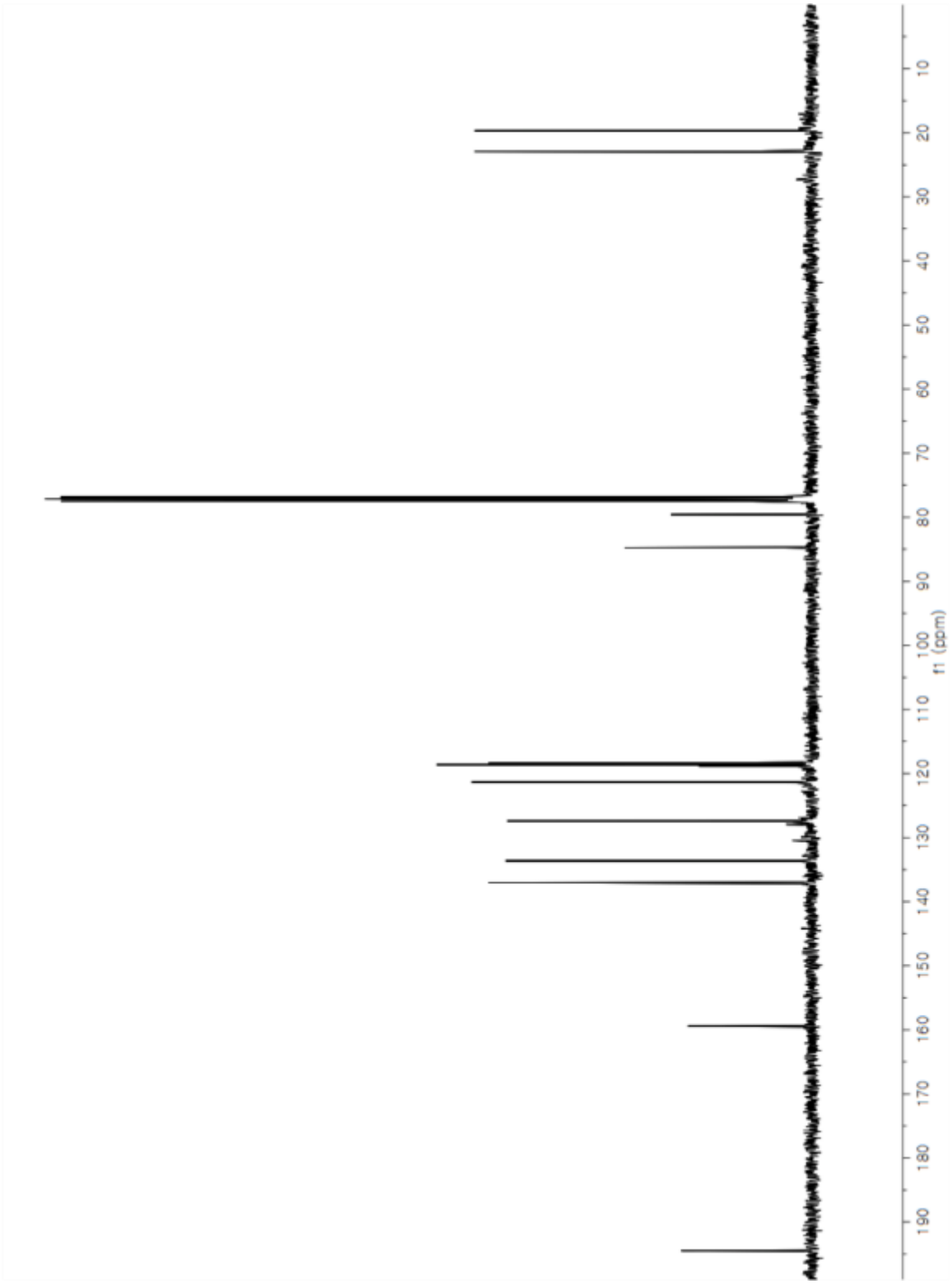
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (ddd, *J* = 7.8 Hz, 1.8 Hz, 0.4 Hz 1H), 7.53 (ddd, *J* = 8.4 Hz, 7.2 Hz, 1.8 Hz, 1H), 7.02 (ddd, *J* = 7.8 Hz, 7.2 Hz, 1.0 Hz, 1H), 6.95 (ddd, *J* = 8.4 Hz, 1.0 Hz, 0.4 H,z 1H), 6.11 (dd, *J* = 17.0 Hz, 10.6 Hz, 1H), 5.64 (dd, *J* = 17.0 Hz, 1.5 Hz, 1H), 5.31 (dd, *J* = 10.6 Hz, 1.5 Hz, 1H), 3.96 (s, 1H), 1.46 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 159.5, 137.1, 133.6, 127.4, 121.4, 118.8, 118.6, 118.3, 84.7, 79.6, 22.9, 19.7.

LRMS (CI) Calcd. for $C_{13}H_{14}O_3$ $[M+H]^+$: 219, Found: 219.

FTIR (neat): 3474, 1692.


3.19
3.12
0.98
1.02
1.04
1.00
1.02
1.05
1.02
1.02
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
f1 (ppm)


10
20
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60
70
80
90
100
110
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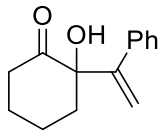
130
140
150
160
170
180
190
f1 (ppm)

2-Hydroxy-2-(1-phenylvinyl)cyclohexan-1-one (4.3s)



The reaction (0.2 mmol scale) was conducted with 500 mol% of 1-phenylvinyl 2,2,2-triphenylacetate at 150 °C for a 24 hour period in accordance with the general procedure. Flash column chromatography (SiO_2, 35% DCM/hexanes to 65% DCM/hexanes, followed by 5% EtOAc/hexanes) provided the title compound (17.3 mg, 40%) as a pale yellow oil.

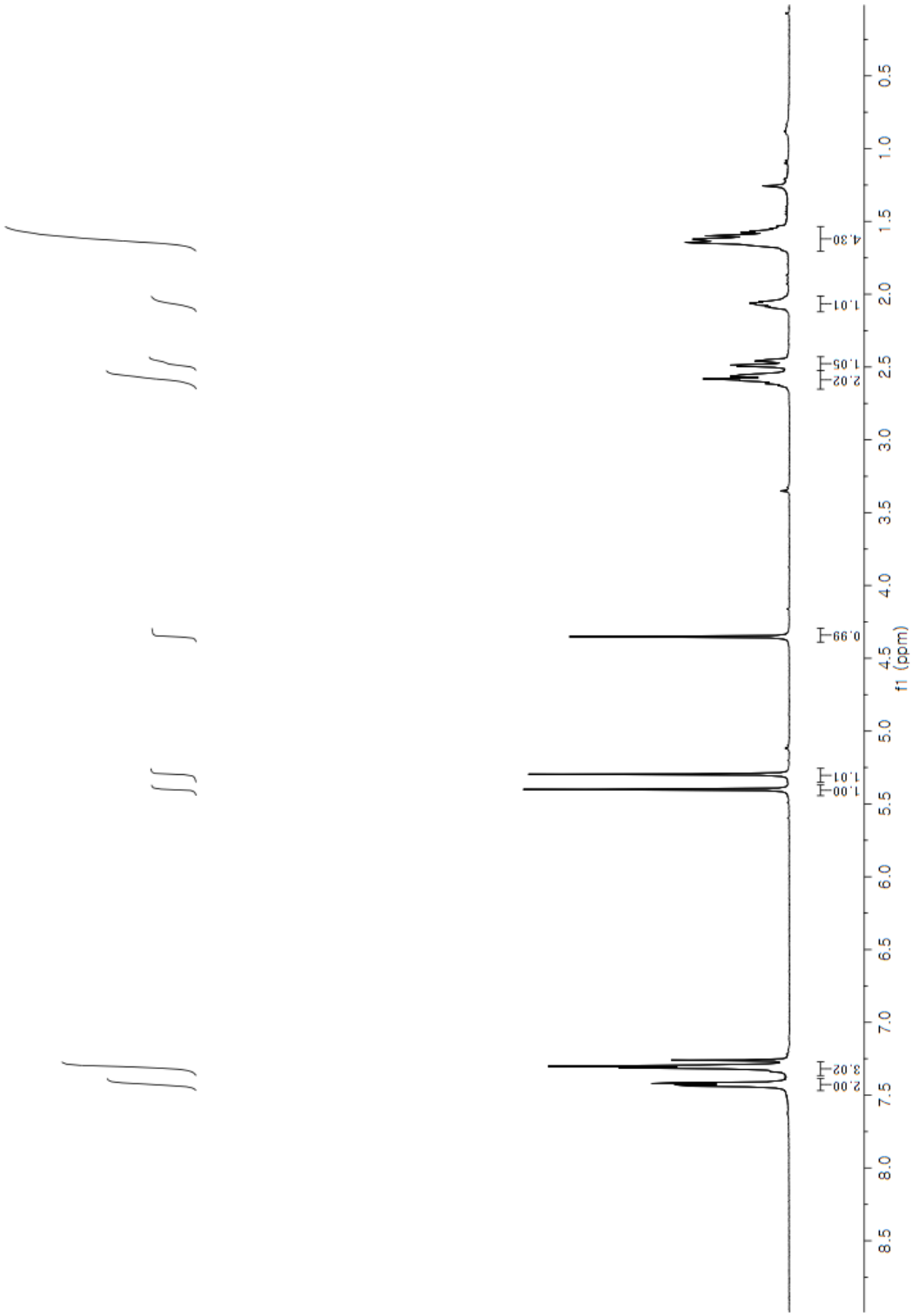
R_f: 0.43 (EtOAc:hexanes = 1:4).

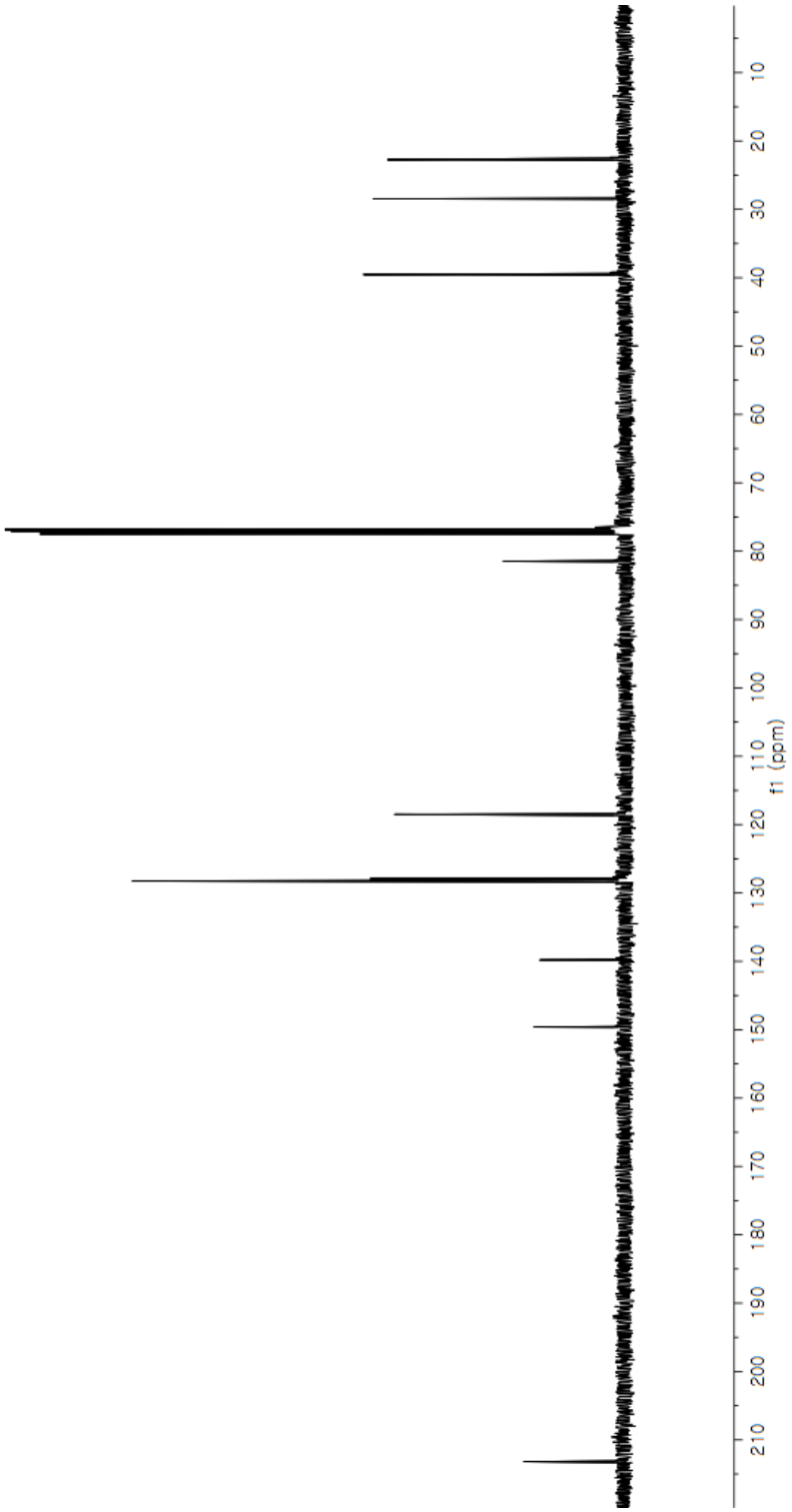
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 6.5 Hz, 3.1 Hz, 2H), 7.37–7.27 (m, 3H), 5.40 (s, 1H), 5.30 (s, 1H), 4.35 (s, 1H), 2.59 (dt, *J* = 9.1 Hz, 6.0 Hz, 2H), 2.52–2.43 (m, 1H), 2.12–2.01 (m, 1H), 1.70–1.54 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 213.2, 149.6, 139.8, 128.4, 128.3, 127.9, 118.5, 81.5, 39.52, 39.48, 28.5, 22.7.

LRMS (ESI) Calcd. for $C_{14}H_{16}O_2$ $[M+Na]^+$: 239, Found: 239.

FTIR (neat): 3470, 2942, 1709.


4.30
1.01
2.02
1.05
0.99
1.00
1.01
2.00
3.02
f1 (ppm)


10
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100
110
120
130
140
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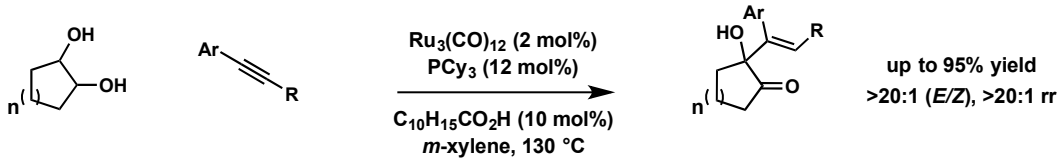
160
170
180
190
200
210
f1 (ppm)

Chapter 5: Ruthenium Catalyzed C-C Coupling of Alkynes to 3-Hydroxy-2-Oxindoles

5.1 Introduction

In exploring ruthenium (0)-catalyzed C-C couplings of secondary alcohols, it was found that 1,2-diols and other vicinally dioxygenated compounds such as α-ketols and 1,2-diones will react with alkynes to form products of vinylation.[51] Such transformation converts secondary alcohols to tertiary allylic alcohols in the form of α-hydroxy-β,γ-unsaturated ketones (**Scheme 5.1**). One limitation of this work was that the alkynes were limited to aryl substituted alkynes. It has been shown that *N*-3-hydroxy-2-oxindoles can react with simple α-olefins reported by Krische and co-workers,[28] and a key factor for this reaction was the highly reactive isatin that is formed *in-situ* and is able to oxidatively couple. The hypothesis was that if such reactivity of *N*-3-hydroxy-2-oxindoles could be used to couple with α-olefins, these *N*-3-hydroxy-2-oxindoles may be able to couple with aryl substituted alkynes and potentially even simple aliphatic alkynes. The ubiquity of the 3-substituted 3-hydroxy-2-oxindoles scaffold in human medicine further motivated this work such it could be used in organic synthesis.[79,80]

Scheme 5.1: Coupling of aryl alkynes to 1,2-diols

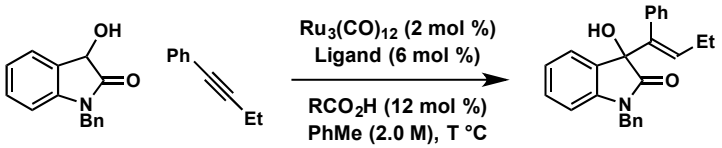


5.2. Reaction Development and Scope

In initial experiments (**Table 5.1**) *N*-benzyl-3-hydroxy-2-oxindole was exposed to 1-phenyl-1-butyne in the presence of $Ru_3(CO)_{12}$ in the absence of ligand returned only trace amount of product, but with the addition of a bidentate phosphine ligand 1,3-

bis(diphenylphosphino) propane (dppp), coupling product was obtained in 54% yield as a single regioisomer **5.3r**. Based on previous work, it has been shown that the use of carboxylic acids enhances yields by cocatalyzing the cleavage of oxaruthenacycles.[28,29] After a screen of assorted carboxylic acids, it was found that 1-adamantane carboxylic acid provided the desired coupling product in 90% yield. Upon further optimization with other mono- and bidentate ligands, it was found that dppp remained the superior ligand in conducting the transformation with alkynes and *N*-benzyl-3-hydroxy-2-oxindole. Lastly, decreasing the catalytic systems loading by half gave the same results and thus providing the deemed optimal conditions.

Table 5.1: Selected optimization experiments for 1-phenyl-1-butyne coupling with *N*-benzyl-3-hydroxy-2-oxindole



5.1a (100 mol %) | **5.2f** (300 mol %) | **5.3f** >20:1 (*E*:*Z*), >20:1 rr

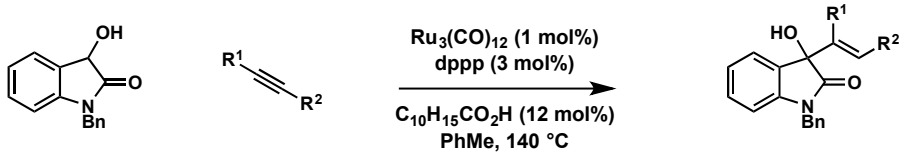
entry	ligand	T °C	RCO_2H	3a (yield)
1	---	140	---	trace
2	dppp	140	---	54%
3	dppp	140	$PhCO_2H$	60%
4	dppp	140	*p*-$NO_2C_6H_4CO_2H$	26%
5	dppp	140	$C_6F_5CO_2H$	71%
6	dppp	140	$C_{10}H_{15}CO_2H$	90%
7	dppe	140	$C_{10}H_{15}CO_2H$	63%
8	dCype	140	$C_{10}H_{15}CO_2H$	39%
9	dppf	140	$C_{10}H_{15}CO_2H$	45%
10	*rac*-BINAP	140	$C_{10}H_{15}CO_2H$	49%
11	BIPHEP	140	$C_{10}H_{15}CO_2H$	59%
12	PCy_3	140	$C_{10}H_{15}CO_2H$	53%
13[a]	dppp	140	$C_{10}H_{15}CO_2H$	90%

[a] $Ru_3(CO)_{12}$ (1mol%), dppp (3 mol%), $C_{10}H_{15}CO_2H$ (12 mol%)

To assess the reaction scope of *N*-benzyl-3-hydroxy-2-oxindole reacting with a variety of alkynes were investigated (**Table 5.2**). Aryl substituted alkynes providing the desired coupling adducts in moderate to excellent yields. Heteroaryl alkynes, such as

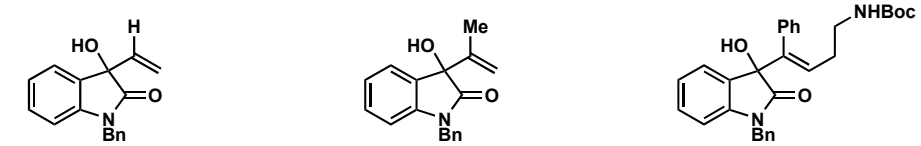
product **5.3e** bearing a thiophene proceeded smoothly and delivered the product in 80% yield. Note that even simple acetylene is able to react and give the product of vinylation in 69% yield **5.2a**. To further probe the reaction scope, electron-donating and halogen substituted *N*-benzyl-3-hydroxy-2-oxindoles were coupled with 1-phenylpropyne (**Table 5.3**) and the corresponding adducts were obtained in good to excellent yields.

Table 5.2: Ruthenium-catalyzed coupling of alkynes to *N*-benzyl-3-hydroxy-2-oxindoles

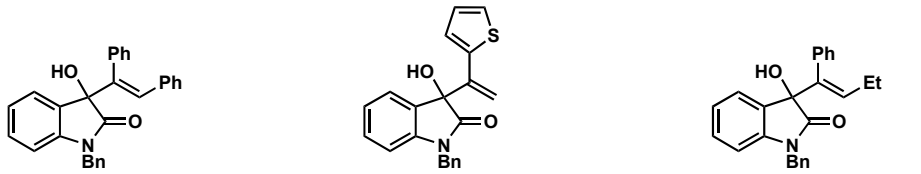


5.1a (100 mol%) | **5.2a-i** (300 mol%) | **5.3a-i** >20:1 (*E*:*Z*), >20:1 rr

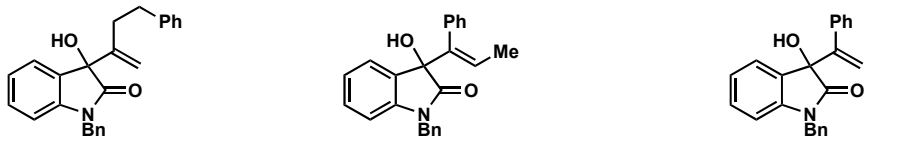
R^1 = H, R^2 = H, 5.2.a	R^1 = Me, R^2 = H, 5.2.b	R^1 = Ph, R^2 = $(CH_2)_2$NHBoc, 5.2.c
R^1 = Ph, R^2 = Ph, 5.2.d	R^1 = 2-thienyl, R^2 = H, 5.2.e	R^1 = Ph, R^2 = Et, 5.2.f
R^1 = $(CH_2)_2$Ph, R^2 = H, 5.2.g	R^1 = Ph, R^2 = Me, 5.2.h	R^1 = Ph, R^2 = H, 5.2.i



5.3a, 69% Yield | **5.3b, 90% Yield** | **5.3c, 60% Yield**

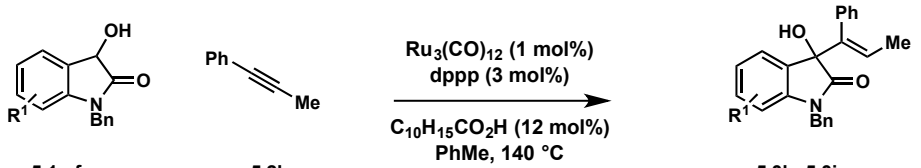


5.3d, 87% Yield,(X-ray) | **5.3e, 80% Yield** | **5.3f, 90% Yield**



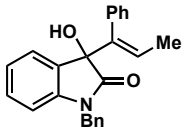
5.3g, 70% Yield | **5.3h, 84% Yield** | **5.3i, 90% Yield**

Table 5.3: Ruthenium-catalyzed coupling of 1-phenylpropyne to substituted *N*-benzyl-3-hydroxy-2-oxindoles

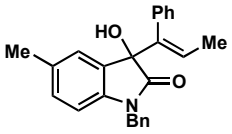


5.1a-f (100 mol%) | 5.2h (300 mol%) | 5.3h, 5.3j-n >20:1 (*E*:*Z*), >20:1 rr

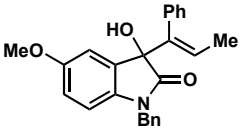
R^1 = H, 5.1a	R^1 = 5-Me, 5.1b	R^1 = 5-MeO, 5.1c
R^1 = 6-Cl, 5.1d	R^1 = 7-F, 5.1e	R^1 = 7,7-Me2-3,7-dihydropyran, 5.1f



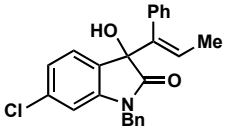
5.3h, 84% Yield



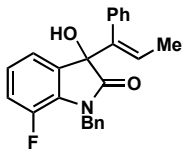
5.3j, 84% Yield



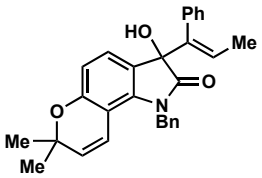
5.3k, 87% Yield



5.3l, 73% Yield



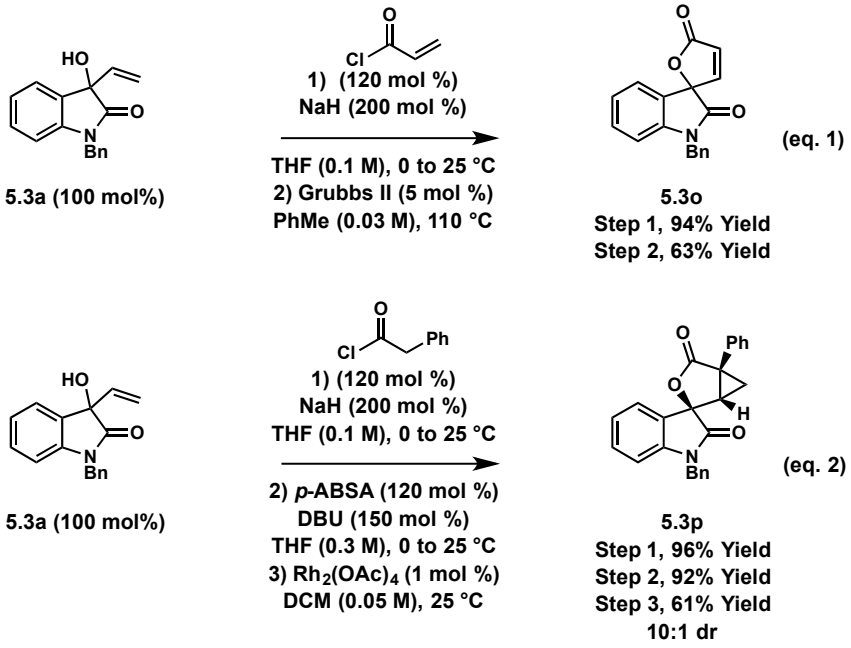
5.3m, 87% Yield



5.3n, 73% Yield

To illustrate the utility of the coupling products, compound **5.3a** was subjected to two different sets of chemical transformations that provided compounds **5.3o** and **5.3p** (**Scheme 5.2**). In the first of chemical transformations **5.3a** was converted into an α,β-unsaturated lactone **5.3o**.[81] Compound **5.3a** was then converted to the *syn*-cyclopropane adduct **5.3p** *via* rhodium catalyzed intramolecular cyclopropanation[82] with good selectivity and stereochemistry for the compound was verified by NOE studies.

Scheme 5.2: Product elaborations of **5.3a**



5.3 CONCLUSION

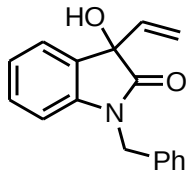
In summary, by harnessing the reducing power of alcohols one can bypass the use of premetalated reagents in carbonyl addition.[83,84] The use of a ruthenium (0) catalyst to couple aryl and aliphatic alkynes to form products of vinylation. Using simple alkynes such as acetylene is also well tolerated. Future work will be focused on the development of other catalytic systems that will allow access to other chemical feedstocks and use them as pronucleophiles in redox-triggered carbonyl addition via alcohol mediated hydrogen transfer.

5.4 EXPERIMENTAL SECTION

General Information: All reactions were run under an atmosphere of argon unless otherwise stated. Toluene was distilled from sodium/benzophenone under a nitrogen atmosphere and transferred via an oven-dried syringe. Resealable pressure tubes were oven-dried and cooled under a stream of argon. Pressure tubes were purchased from Fisher Scientific (catalog number 14-959-35C). *N*-benzyl-3-hydroxyindolin-2-one **5.1a** was prepared via $NaBH_4$ reduction of 1-benzylindoline-2,3-dione.[85,86] $Ru_3(CO)_{12}$, 1,3-bis(diphenylphosphino)propane (DPPP), alkynes **5.2a, 5.2b, 5.2d-5.2i** and 1-adamantanecarboxylic acid were used as received from commercial suppliers. Alkyne **5.2c** was synthesized according to the literature.[87] Preparative column chromatography employing silica gel was performed according to the method of Still.[49] Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Adsorbents F254). Visualization was accomplished with UV light followed by dipping in a p-anisaldehyde solution and heating. Infrared spectra were recorded on a Thermo Nicolet 380 spectrometer. Low-resolution mass spectra (LRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+Na, M+H, M or M-H) or a suitable fragment ion. Melting points were obtained on a Stuart SMP3 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini (400 MHz) spectrometer at ambient temperature unless otherwise noted. Chemical shifts are reported in delta (δ) units, parts per million (ppm), relative to the center of the singlet at 7.26 ppm for deuterochloroform. Data are reported as: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in Hz and integration. ^{13}C NMR spectra were recorded on a Varian Gemini (100 MHz) spectrometer and were routinely run with broadband

decoupling. Chemical shifts are reported in ppm, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm).

1-Benzyl-3-hydroxy-3-vinylindolin-2-one (5.3a)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with acetylene **5.2a**. Toluene (0.15 mL, 2.0 M concentration with respect to **5.1a**) was added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 ^oC (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 9:1) to furnish the title compound **5.3a** (55 mg, 0.21 mmol) as an orange solid in 69% yield.

TLC (SiO_2): R_f= 0.30 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.34-7.25 (m, 5H), 7.22(dt, *J* = 7.8, 1.2 Hz, 1H), 7.08 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.07 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.46 (dd, *J* = 17.2, 0.8 Hz, 1H), 5.35 (dd, *J* = 10.6, 0.8 Hz, 1H), 5.00 (d, *J* = 15.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 3.58 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 142.4, 136.2, 135.3, 129.8, 129.3, 128.8, 127.7, 127.1, 124.8, 123.4, 116.9, 109.7, 77.2, 43.8.

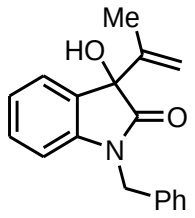
MP: 169-170 ^{o}C

LRMS (ESI): Calcd. for $C_{17}H_{15}NO_2$ $[M+Na]^+$: 288, Found: 288.

FTIR (neat): 3334, 1687, 1611, 1466, 1350, 1176, 905 cm^{-1}.

177.1
142.4
136.2
135.3
129.8
129.3
128.8
127.7
127.1
124.8
123.4
116.9
109.7
77.2
43.8
220
200
180
160
140
120
100
80
60
40
20
0
ppm

1-Benzyl-3-hydroxy-3-(prop-1-en-2-yl)indolin-2-one (5.3b)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with propyne **5.2b**. Toluene (0.15 mL, 2.0 M concentration with respect to **5.1a**) was added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 9:1) to furnish the title compound **5.3b** (75 mg, 0.27 mmol) as an orange solid in 90% yield.

TLC (SiO_2): R_f= 0.41 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.19 (m, 6H), 7.17 (dt, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.01 (dt, *J* = 7.6 Hz, 1.0 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 5.42 (app. t, *J* = 0.8 Hz, 1H), 5.09 (app. t, *J* = 1.2 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H), 4.73 (d, *J* = 15.6 Hz, 1H), 3.16 (s, 1H), 1.55 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 143.1, 142.8, 135.4, 129.8, 129.4, 128.8, 127.7, 127.3, 124.3, 123.4, 112.7, 109.6, 79.3, 44.0, 18.0.

MP: 125-126 °C

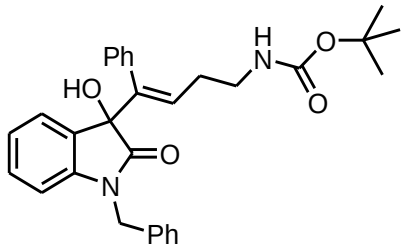
LRMS (ESI): Calcd. for $C_{18}H_{17}NO_2$ $[M+Na]^+$: 302, Found: 302.

FTIR (neat): 3317, 3060, 2977, 2360, 2342, 1697, 1613, 1468, 1372, 1171, 972 cm^{-1}.

7.29
7.28
7.27
7.25
7.23
7.21
7.19
7.19
7.17
7.17
7.15
7.15
7.03
7.02
7.01
7.01
6.99
6.99
6.70
6.68
5.42
5.09
5.03
4.99
4.74
4.70
3.16
1.55
6.18
1.04
1.02
1.01
1.00
1.00
1.00
1.01
0.99
3.05
ppm

177.1
143.1
142.8
135.4
129.8
129.4
128.8
127.7
127.3
124.3
123.4
112.7
109.6
79.3
44.0
18.0
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*E*)-tert-butyl4-(1-benzyl-3-hydroxy-2-oxoindolin-3-yl)-4-phenylbut-3 enylcarbamate (5.3c)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), alkyne **5.2c** (0.22 g, 0.90 mmol, 300 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Toluene (0.15 mL, 2.0 M concentration with respect to **5.1a**) was added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 ^oC (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to furnish the title compound **5.3c** (87 mg, 0.18 mmol) as a white solid in 60% yield.

TLC (SiO_2): R_f= 0.20 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.25–7.21 (m, 1H), 7.17-7.06 (m, 7H), 6.73 (d, *J* = 6.8 Hz, 2H), 6.54 (d, *J* = 7.2 Hz, 2H), 6.44 (t, *J* = 7.6 Hz, 1H), 6.40 (d, *J* = 7.6 Hz, 1H), 5.03 (d, *J* = 16.0 Hz, 1H), 4.66 (t, *J* = 5.4 Hz, 1H), 4.33 (d, *J* = 16.0 Hz, 1H), 3.74 (s, 1H), 3.18-3.15 (m, 2H), 2.06-2.00 (m, 2H), 1.42 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 155.9, 143.1, 141.7, 135.7, 134.8, 129.9, 129.2, 128.6, 128.1, 127.3, 127.2, 126.4, 125.7, 124.6, 123.2, 109.6, 79.7, 79.1, 43.8. 40.1, 29.2, 28.4.

MP: 169-170 °C

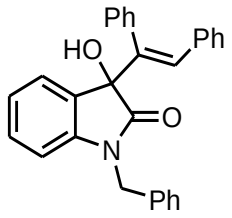
LRMS (ESI): Calcd. for $C_{30}H_{32}N_2O_4$ $[M+Na]^+$: 507, Found: 507.

FTIR (neat): 3339, 2931, 1699, 1613, 1489, 1168, 1100, 980 cm^{-1}.

7.41
7.39
7.24
7.23
7.21
7.16
7.14
7.12
7.10
7.08
7.06
6.74
6.72
6.55
6.53
6.48
6.46
6.44
6.40
6.39
5.06
5.02
4.73
4.35
4.31
4.03
3.18
3.16
3.15
3.14
3.13
2.05
2.04
2.04
2.02
2.00
1.42
9.05
2.01
2.11
0.86
1.03
0.97
1.08
1.09
1.17
7.26
2.01
2.10
1.01
1.02
ppm

177.0
155.9
143.1
141.7
135.7
134.8
129.9
129.2
128.6
128.1
127.3
127.2
126.4
125.7
124.6
123.2
109.6
79.7
79.1
43.8
40.1
29.2
28.4
0
20
40
60
80
100
120
140
160
180
200
220
ppm

(*E*)-1-Benzyl-3-(1,2-diphenylvinyl)-3-hydroxyindolin-2-one (5.3d)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%), 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%) and alkyne **5.2d** (0.16 g, 0.90 mmol, 300 mol%). The tube was sealed with a rubber septum and purged with argon. Toluene (0.15 mL, 2.0 M concentration with respect to **5.1a**) was added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 9:1) to furnish the title compound **5.3d** (109 mg, 0.26 mmol) as a white solid in 87% yield.

TLC (SiO_2): R_f= 0.38 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.42 (s, 1H), 7.29-7.25 (m, 1H), 7.20-7.05 (m, 10H), 6.91-6.89 (m, 2H), 6.81 (d, *J* = 7.6 Hz, 2H), 6.59 (d, *J* = 7.2 Hz, 2H), 6.44(d, *J* = 7.6 Hz, 1H), 5.05 (d, *J* = 15.8 Hz, 1H), 4.35 (d, *J* = 15.8 Hz, 1H), 3.60 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 143.3, 139.9, 136.3, 135.8, 134.8, 130.0, 130.0, 129.5, 129.3, 128.6, 128.6, 127.6, 127.3, 127.2, 127.1, 126.5, 124.7, 123.3, 109.7, 80.4, 43.9.

MP: 161-162 °C

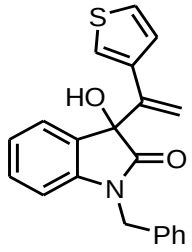
LRMS (ESI): Calcd. for $C_{29}H_{23}NO_2$ $[M+Na]^+$: 440, Found: 440.

FTIR (neat): 3317, 3029, 2970, 2359, 2342, 1738, 1703, 1690, 1612, 950 cm^{-1}.

7.50
7.48
7.42
7.29
7.27
7.26
7.25
7.19
7.17
7.16
7.14
7.12
7.11
7.10
7.08
7.07
7.06
6.91
6.90
6.90
6.89
6.82
6.80
6.60
6.58
6.45
6.43
5.07
5.03
4.37
4.33
3.60
1.02
1.00
1.38
10.17
2.05
1.98
2.01
1.00
1.00
1.00
1.03
10
9
8
7
6
5
4
3
2
1
0
ppm

177.0
143.3
139.9
136.3
135.8
134.8
130.0
130.0
129.5
129.3
128.6
128.6
128.0
127.6
127.3
127.2
127.1
126.5
124.7
123.3
109.7
80.4
43.9
ppm

1-Benzyl-3-hydroxy-3-(1-(thiophen-3-yl)vinyl)indolin-2-one (5.3e)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%).The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2e** (0.09 mL, 0.90 mmol, 300 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 ^oC (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 9:1) to furnish the title compound **5.3e** (83 mg, 0.24 mmol) as a yellow solid in 80% yield.

TLC (SiO_2): R_f= 0.34 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.25-7.21 (m, 4H), 7.11-7.06 (m, 2H), 6.97-6.94 (m, 2H), 6.72-6.69 (m, 2H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.93 (d, *J* = 1.0 Hz, 1H), 5.52 (d, *J* = 1.0 Hz, 1H), 5.07 (d, *J* = 15.8 Hz, 1H), 4.54 (d, *J* = 15.8 Hz, 1H), 3.47 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 143.4, 142.7, 138.4, 135.0, 130.2, 129.4, 128.8, 128.2, 127.5, 127.0, 125.0, 124.7, 123.4, 123.0, 115.8, 109.7, 78.7, 44.0.

MP: 175-176 °C

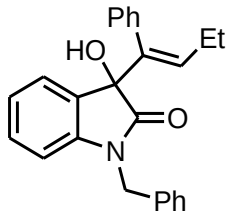
LRMS (ESI): Calcd. for $C_{21}H_{17}NO_2S$ $[M+Na]^+$: 370, Found: 370.

FTIR (neat): 3403, 2970, 2359, 2342, 1699, 1609, 1369, 1179, 977 cm^{-1}.

3.47
4.52
4.56
5.06
5.10
5.52
5.52
5.94
5.94
6.64
6.66
6.69
6.71
6.71
6.72
6.72
6.95
6.96
6.97
7.06
7.08
7.09
7.10
7.10
7.11
7.21
7.21
7.23
7.23
7.24
7.35
7.37
0.98
1.00
1.01
1.00
1.00
0.99
1.97
1.97
2.05
3.99
1.03
ppm

176.6
143.4
142.7
138.4
135.0
130.2
129.4
128.8
128.2
127.5
127.0
125.0
124.7
123.4
123.0
115.8
109.7
78.7
44.0
0
20
40
60
80
100
120
140
160
180
200
220
ppm

(*E*)-1-Benzyl-3-hydroxy-3-(1-phenylbut-1-enyl)indolin-2-one (5.3f)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2f** (0.13 mL, 0.90 mmol, 300 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 ^oC (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 9:1) to furnish the title compound **5.3f** (99 mg, 0.27 mmol) as a white solid in 90% yield.

TLC (SiO_2): R_f= 0.43 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.26–7.21 (m, 1H), 7.18-7.06 (m, 7H), 6.77 (d, *J* = 7.2 Hz, 2H), 6.58 (d, *J* = 7.2 Hz, 2H), 6.43-6.40 (m, 2H), 5.05 (d, *J* = 16.0 Hz, 1H), 4.34 (d, *J* = 16.0 Hz, 1H), 3.29 (s, 1H), 1.86 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ□177.1, 143.1, 138.6, 136.1, 134.9, 130.7, 130.0, 129.8, 129.5, 128.6, 128.0, 127.2, 126.5, 124.6, 123.1, 109.5, 79.6, 43.7, 21.9, 14.3.

MP: 141-142 °C

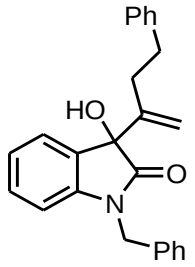
LRMS (ESI): Calcd. for $C_{25}H_{23}NO_2$ $[M+Na]^+$: 392, Found: 392.

FTIR (neat): 3345, 2958, 2360, 2342, 1705, 1612, 1173, 984 cm^{-1}.

0.95
0.97
0.99
1.81
1.83
1.85
1.87
1.89
3.29
4.32
4.36
5.03
5.07
6.40
6.40
6.42
6.42
6.42
6.57
6.57
6.59
6.59
6.59
6.75
6.77
7.08
7.08
7.10
7.10
7.11
7.11
7.12
7.12
7.13
7.13
7.14
7.14
7.15
7.15
7.16
7.16
7.16
7.22
7.24
7.38
7.39
7.40
7.41
3.06
2.05
1.00
1.00
1.00
2.01
1.99
1.95
7.15
1.05
1.01
ppm

14.3
21.9
43.7
79.6
109.5
123.1
124.6
126.5
127.1
127.2
128.0
128.6
129.5
129.8
130.0
130.7
134.9
136.2
138.6
143.1
177.1
0
20
40
60
80
100
120
140
160
180
200
220
ppm

1-Benzyl-3-hydroxy-3-(4-phenylbut-1-en-2-yl)indolin-2-one (5.3g)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2g** (0.13 mL, 0.90 mmol, 300 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 9:1) to furnish the title compound **5.3g** (78 mg, 0.21 mmol) as a white solid in 70% yield.

TLC (SiO_2): R_f=0.40 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.16 (m, 10H), 7.09-7.02 (m, 3H), 6.75(d, *J* = 8 Hz, 1H), 5.71(s, 1H), 5.28(s, 1H), 5.08 (d, *J* = 16.0 Hz, 1H), 4.76 (d, *J* = 16.0 Hz, 1H), 3.29(s, 1H), 2.77 (ddd, *J* = 14.8, 11.0, 5.4 Hz, 1H), 2.64 (ddd, *J* = 14.8, 11.0, 5.4 Hz, 1H), 2.22 (ddd, *J* = 14.8, 11.0, 5.4 Hz, 1H), 2.02 (ddd, *J* = 14.8, 11.0, 5.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 146.6, 143.1, 141.4, 135.4, 129.9, 129.7, 128.8, 128.3, 128.2, 127.7, 127.3, 125.9, 124.5, 123.4, 111.3, 109.6, 79.4, 44.0, 34.0, 32.1.

MP: 156-157 °C

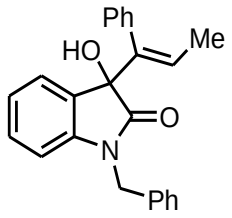
LRMS (ESI): Calcd. for $C_{25}H_{23}NO_2$ $[M+Na]^+$: 392, Found: 392.

FTIR (neat): 3350, 3051, 2943, 2360, 2342, 1698, 1613, 1370, 969 cm^{-1}.

7.30
7.28
7.24
7.22
7.20
7.18
7.09
7.07
7.05
7.04
7.02
6.76
6.75
5.71
5.28
5.10
5.07
4.78
4.74
3.29
2.81
2.80
2.77
2.75
2.74
2.67
2.66
2.65
2.63
2.61
2.60
2.26
2.22
2.20
2.19
2.18
2.06
2.04
2.03
2.02
2.00
1.99
1.97
10.26
3.14
1.00
1.01
1.02
1.01
1.00
0.98
1.05
1.02
1.04
1.04
ppm

177.3
146.6
143.1
141.4
135.4
129.9
129.7
128.8
128.3
128.2
127.7
127.3
125.9
124.5
123.4
111.3
109.6
79.4
44.0
34.0
32.1
220
200
180
160
140
120
100
80
60
40
20
0
ppm

(*E*)-1-Benzyl-3-hydroxy-3-(1-phenylprop-1-enyl)indolin-2-one (5.3h)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2h** (0.11 mL, 0.90 mmol, 300 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 9:1) to furnish the title compound **5.3h** (90 mg, 0.25 mmol) as a white solid in 84% yield.

TLC (SiO_2): R_f= 0.42 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.24–7.22 (m, 1H), 7.18-7.05 (m, 7H), 6.76 (d, *J* = 6.8 Hz, 2H), 6.59 (d, *J* = 6.8 Hz, 2H), 6.49 (q, *J* = 6.8 Hz, 1H), 6.42 (d, *J* = 7.2 Hz, 1H), 5.04 (d, *J* = 16.0 Hz, 1H), 4.36 (d, *J* = 16.0 Hz, 1H), 3.12 (s, 1H), 1.52 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 143.1, 139.9, 136.1, 134.9, 130.0, 129.7, 129.5, 128.6, 128.0, 127.2, 127.1 126.5, 124.6, 123.6, 123.1, 109.6, 79.8, 43.7, 14.2.

MP: 157-158 ^{o}C

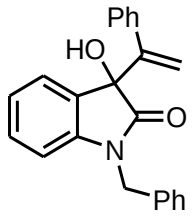
LRMS (ESI): Calcd. for $C_{24}H_{21}NO_2$ $[M+Na]^+$: 378, Found: 378.

FTIR (neat): 3356, 3059, 2911, 2360, 1697, 1168 cm^{-1}.

7.40
7.40
7.38
7.38
7.26
7.24
7.22
7.17
7.15
7.13
7.12
7.09
7.08
7.06
6.77
6.76
6.60
6.58
6.52
6.50
6.49
6.47
6.43
6.41
5.06
5.02
4.38
4.34
3.12
1.53
1.52
0.99
1.02
7.10
1.96
1.98
0.99
0.99
1.01
1.00
0.96
3.00
ppm

177.2
143.1
139.9
136.1
134.9
130.0
129.7
129.5
128.6
128.0
127.2
127.1
126.5
124.6
123.6
123.1
109.6
79.8
43.7
14.2
220
200
180
160
140
120
100
80
60
40
20
0
ppm

1-Benzyl-3-hydroxy-3-(1-phenylvinyl)indolin-2-one (5.3i)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxyindolin-2-one **5.1a** (72 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2i** (0.10 mL, 0.90 mmol, 300 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1a**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 9:1) to furnish the title compound **5.3i** (61 mg, 0.18 mmol) as a white solid in 60% yield.

TLC (SiO_2): R_f= 0.40 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.24–7.07 (m, 8H), 6.89-6.86 (m, 2H), 6.73-6.71 (m, 2H), 6.53 (d, *J* = 7.6 Hz, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 5.38 (d, *J* = 1.0 Hz, 1H), 5.06 (d, *J* = 15.8 Hz, 1H), 4.43 (d, *J* = 15.8 Hz, 1H), 3.27 (s, 1H).

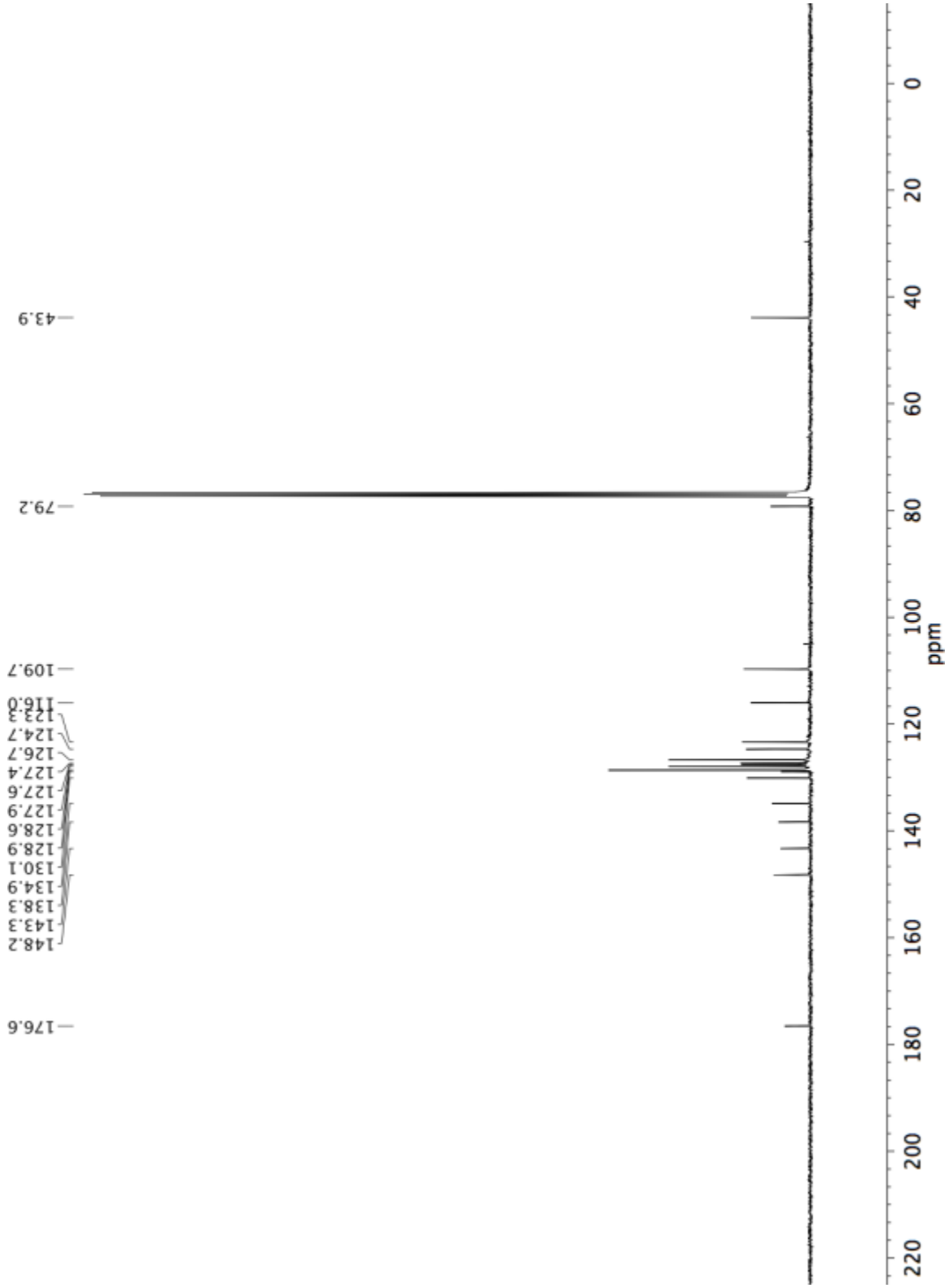
^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 148.2, 143.3, 138.3, 134.9, 130.1, 128.9, 128.6, 127.9, 127.6, 127.4, 126.7, 124.7, 123.3, 116.0, 109.7, 79.2, 43.9.

MP: 115-116 ^{o}C

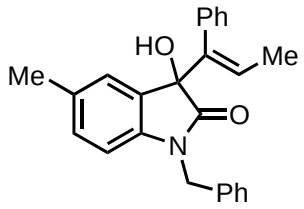
LRMS (ESI): Calcd. for $C_{23}H_{19}NO_2$ $[M+Na]^+$: 364, Found: 364.

FTIR (neat): 3398, 3057, 2922, 2360, 1702, 1610, 1489, 1178, 913 cm^{-1}.

7.41
7.40
7.39
7.39
7.24
7.22
7.19
7.17
7.17
7.16
7.14
7.13
7.11
7.11
7.10
7.09
7.09
6.88
6.88
6.86
6.86
6.73
6.71
6.71
6.54
6.52
6.01
6.01
5.38
5.38
5.08
5.04
4.45
4.41
3.27
1.08
8.07
2.00
2.00
2.00
1.00
0.99
0.99
1.00
1.01
1.00
ppm
10
9
8
7
6
5
4
3
2
1
0


43.9
79.2
109.7
116.0
123.3
124.7
126.7
127.4
127.6
127.9
128.6
128.9
130.1
134.9
138.3
143.3
148.2
176.6
0
20
40
60
80
100
120
140
160
180
200
220
ppm

(*E*)-1-benzyl-3-hydroxy-5-methyl-3-(1-phenylprop-1-en-1-yl)indolin-2-one (5.3j)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxy-5-methylindolin-2-one **5.1b** (76 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2h** (0.11 mL, 0.90 mmol, 300 mol%), 2-propanol (92 μL, 0.6 mmol, 200 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1b**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to furnish the title compound **5.3j** (93 mg, 0.25 mmol) as a white solid in 84% yield.

TLC (SiO_2): R_f= 0.33 (EtOAc/Hexanes=1/2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.20 (m, 2H), 7.19 – 7.06 (m, 5H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.80 – 6.75 (d, *J* = 6.9 Hz, 2H), 6.63 – 6.57 (d, *J* = 6.3 Hz, 2H), 6.54 – 6.45 (q, *J* = 6.9 Hz, 1H), 6.31 (d, *J* = 7.9 Hz, 1H), 5.01 (d, *J* = 16.0 Hz, 1H), 4.34 (d, *J* = 16.0 Hz, 1H), 3.26 (s, 1H), 2.33 (s, 3H), 1.53 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 140.8, 140.2, 136.13, 135.0, 132.7, 130.0, 130.0, 129.4, 128.5, 128.0, 127.1, 127.1, 126.5, 125.3, 123.4, 109.3, 79.8, 43.8, 21.0, 14.1.

M.P. 161-162 °C

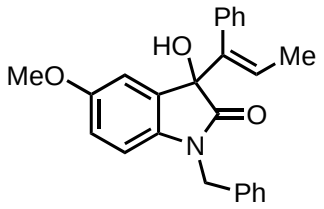
LRMS (ESI): Calcd. for $C_{25}H_{23}NO_2$ $[M+Na]^+$: 392, Found: 392.

FTIR (neat): 3327, 3027, 2910, 2855, 1700, 1493, 1145, 693 cm^{-1}.

7.25
7.24
7.23
7.22
7.18
7.16
7.16
7.14
7.13
7.11
7.09
6.95
6.93
6.79
6.77
6.60
6.58
6.52
6.50
6.48
6.47
6.32
6.30
5.03
4.99
4.36
4.32
3.26
2.33
1.54
1.53
1.97
5.12
1.06
2.00
1.98
0.99
0.95
1.00
1.00
0.93
3.04
3.08
ppm

177.0
140.8
140.2
136.1
135.0
132.7
130.0
130.0
129.4
128.5
128.0
127.1
127.1
126.5
125.3
123.4
109.3
79.8
43.8
21.0
14.1
ppm

(*E*)-1-benzyl-3-hydroxy-5-methoxy-3-(1-phenylprop-1-en-1-yl)indolin-2-one (5.3k)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxy-5-methoxyindolin-2-one **5.1c** (81 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2h** (0.11 mL, 0.90 mmol, 300 mol%), 2-propanol (92 μL, 0.6 mmol, 200 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1c**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to furnish the title compound **5.3k** (101 mg, 0.26 mmol) as a white solid in 87% yield.

TLC (SiO_2): R_f= 0.25 (EtOAc/Hexanes=1/2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.23 (m, 1H), 7.20 – 7.10 (m, 5H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.81 (d, *J* = 7.1 Hz, 2H), 6.67 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.60 (d, *J* = 6.7 Hz, 2H), 6.49 (q, *J* = 6.8 Hz, 1H), 6.31 (d, *J* = 8.5 Hz, 1H), 5.01 (d, *J* = 16.0 Hz, 1H), 4.34 (d, *J* = 16.0 Hz, 1H), 3.78 (s, 3H), 3.35 (s, 1H), 1.53 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 156.3, 140.1, 136.5, 136.0, 135.0, 130.7, 130.0, 128.6, 128.0, 127.2, 127.1, 126.5, 123.7, 114.7, 111.3, 110.1, 80.0, 55.8, 43.9, 14.1.

M.P. 193-194 °C

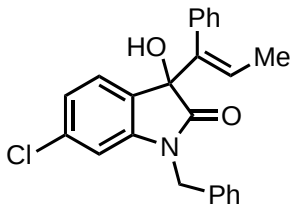
LRMS (ESI): Calcd. for $C_{25}H_{23}NO_3$ $[M+Na]^+$: 408, Found: 408.

FTIR (neat): 3342, 2928, 1697, 1604, 1490, 1346, 1183, 770 cm^{-1}.

1.54
1.52
3.35
3.78
4.36
4.32
5.04
4.99
6.31
6.33
6.47
6.49
6.51
6.52
6.60
6.61
6.66
6.66
6.68
6.68
6.80
6.82
6.99
7.00
7.12
7.14
7.15
7.17
7.19
7.23
7.25
7.27
3.01
0.99
2.98
1.00
1.00
0.93
0.93
1.94
1.18
2.01
1.06
4.96
1.08
0
1
2
3
4
5
6
7
8
9
10
ppm

14.1
43.9
55.8
80.0
110.1
111.3
114.7
123.7
126.5
127.1
127.2
128.0
128.6
130.0
130.7
135.0
136.0
136.5
140.1
156.3
176.9
0
20
40
60
80
100
120
140
160
180
200
220
ppm

***(E)*-1-benzyl-6-chloro-3-hydroxy-3-(1-phenylprop-1-en-1-yl)indolin-2-one (5.3l)**



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-6-chloro-3-hydroxyindolin-2-one **5.1d** (82 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2h** (0.11 mL, 0.90 mmol, 300 mol%), 2-propanol (92 μL, 0.6 mmol, 200 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1d**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to furnish the title compound **5.3l** (85 mg, 0.22 mmol) as a white solid in 73% yield.

TLC (SiO_2): R_f= 0.46 (EtOAc/Hexanes=1/2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.23 (m, 2H), 7.21 – 7.12 (m, 5H), 7.05 (dd, *J* = 7.9, 1.8 Hz, 1H), 6.78 (d, *J* = 6.9 Hz, 2H), 6.62 – 6.58 (m, 2H), 6.49 (q, *J* = 6.8 Hz, 1H), 6.42 (d, *J* = 2.0 Hz, 1H), 5.00 (d, *J* = 0.8 Hz, 1H), 4.33 (d, *J* = 16.0 Hz, 1H), 3.43 (s, 1H), 1.52 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 144.3, 139.6, 135.8, 135.4, 134.3, 130.0, 128.7, 128.2, 128.0, 127.4, 127.3, 126.4, 125.6, 124.1, 123.1, 110.1, 79.3, 43.8, 14.1.

M.P. 166-167 °C

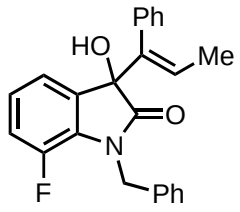
LRMS (ESI): Calcd. For $C_{24}H_{20}ClNO_2$ $[M+Na]^+$: 412, Found: 412.

FTIR (neat): 3372, 3063, 2911, 1701, 1610, 1487, 1453, 906 cm^{-1}.

7.30
7.28
7.25
7.24
7.24
7.21
7.20
7.19
7.18
7.18
7.17
7.16
7.15
7.14
7.13
7.12
7.12
7.07
7.06
7.05
7.04
6.79
6.79
6.77
6.77
6.61
6.59
6.52
6.50
6.48
6.47
6.43
5.03
4.99
4.35
4.31
3.43
1.53
1.51
3.04
1.01
1.00
1.00
0.95
1.07
1.96
1.96
1.01
5.28
2.27
ppm

14.1
43.8
79.3
110.1
123.1
124.1
125.6
126.4
127.3
127.4
128.0
128.2
128.7
130.0
134.3
135.4
135.8
139.6
144.3
177.1
0
20
40
60
80
100
120
140
160
180
200
220
ppm

(*E*)-1-benzyl-7-fluoro-3-hydroxy-3-(1-phenylprop-1-en-1-yl)indolin-2-one (5.3m)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-7-fluoro-3-hydroxyindolin-2-one **5.1e** (77 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2h** (0.11 mL, 0.90 mmol, 300 mol%), 2-propanol (92 μL, 0.6 mmol, 200 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1e**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 ^oC (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to furnish the title compound **5.3m** (104 mg, 0.28mmol) as a white solid in 93% yield.

TLC (SiO_2): R_f= 0.32 (EtOAc/Hexanes=1/2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.11 (m, 7H), 7.07 – 6.99 (m, 1H), 6.93 (ddd, *J* = 11.3, 8.4, 1.1 Hz, 1H), 6.80 – 6.72 (m, 4H), 6.49 (q, *J* = 6.8 Hz, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.68 (d, *J* = 15.5 Hz, 1H), 3.58 (s, 1H), 1.52 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 148.5, 146.1, 139.6, 136.2, 135.7, 132.5, 132.5, 129.9, 129.7, 129.7, 128.4, 128.1, 127.3, 127.1, 126.6, 126.6, 124.1, 123.9, 123.8, 120.7, 120.6, 118.0, 117.8, 79.6, 45.3, 45.2, 14.2.

^{19}F NMR (100 MHz, $CDCl_3$): δ -134.7 (s)

M.P. 153-154 °C

LRMS (ESI): Calcd. for $C_{24}H_{20}FNO_2$ $[M+Na]^+$: 396, Found: 396.

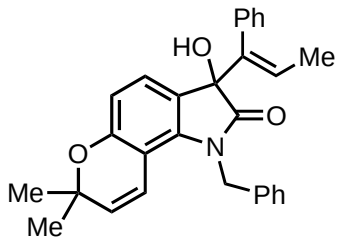
FTIR (neat): 3364, 3064, 2912, 2855, 1698, 1353, 1139, 1024 cm^{-1}.

7.25
7.23
7.21
7.17
7.16
7.14
7.12
7.12
7.04
7.02
7.01
6.95
6.95
6.93
6.93
6.92
6.90
6.90
6.78
6.76
6.74
6.51
6.49
6.48
6.46
5.01
4.97
4.70
4.66
3.58
1.53
1.51
7.37
1.10
1.07
3.98
0.97
1.01
1.00
1.01
3.00
ppm

176.9
148.5
146.1
139.6
136.2
135.7
132.5
132.5
129.9
129.7
129.7
128.4
128.1
127.3
127.1
126.6
126.6
124.1
123.9
123.8
120.7
120.6
118.0
117.8
79.6
45.3
45.2
14.2
ppm
0
20
40
60
80
100
120
140
160
180
200
220

-134.7
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

(*E*)-1-benzyl-3-hydroxy-7,7-dimethyl-3-(1-phenylprop-1-en-1-yl)-1,7 dihydropyrano[2,3-g]indol-2(3H)-one (5.3n)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added 1-benzyl-3-hydroxy-7,7-dimethyl-1,7-dihydropyrano[2,3-g]indol-2(3H)-one **5.1f** (96 mg, 0.30 mmol, 100 mol%), $Ru_3(CO)_{12}$ (1.9 mg, 0.0030 mmol, 1 mol%), DPPP (3.7 mg, 0.009 mmol, 3 mol%) and 1-adamantanecarboxylic acid (6.5 mg, 0.036 mmol, 12 mol%). The tube was sealed with a rubber septum and purged with argon. Alkyne **5.2h** (0.11 mL, 0.90 mmol, 300 mol%), 2-propanol (92 μL, 0.6 mmol, 200 mol%) and toluene (0.15 mL, 2.0 M concentration with respect to **5.1f**) were added and the rubber septum was quickly replaced with a screw cap. The mixture was heated at 140 °C (oil bath temperature) for 48 hours, at which point the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to furnish the title compound **5.3n** (105 mg, 0.24 mmol) as a white solid in 80% yield.

TLC (SiO_2): R_f= 0.27 (EtOAc/Hexanes=1/2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.07 (m, 7H), 6.80 (d, *J* = 8.3 Hz, 2H), 6.62 (d, *J* = 8.2 Hz, 1H), 6.50 (q, *J* = 6.8 Hz, 1H), 6.42 (d, *J* = 8.2 Hz, 2H), 6.04 (d, *J* = 10.1 Hz, 1H), 5.39 (d, *J* = 10.1 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 4.55 (d, *J* = 17.1 Hz, 1H), 3.47 (s, 1H), 1.51 (d, *J* = 6.8 Hz, 3H), 1.36 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 154.9, 140.2, 139.3, 136.3, 136.0, 131.0, 130.2, 128.8, 128.1, 127.2, 126.9, 125.2, 125.0, 123.2, 122.2, 117.2, 111.5, 107.2, 78.8, 75.0, 45.5, 27.6, 26.3, 14.1.

M.P. 169-170 °C

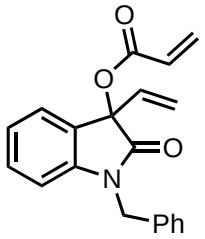
LRMS (ESI): Calcd. for $C_{29}H_{27}NO_3$ $[M+Na]^+$: 460, Found: 460.

FTIR (neat): 3376, 2975, 2923, 1704, 1453, 1360, 1150, 701 cm^{-1}.

7.21
7.20
7.18
7.15
7.13
7.12
7.10
7.08
6.82
6.80
6.64
6.62
6.53
6.52
6.50
6.48
6.43
6.41
6.05
6.03
5.40
5.38
5.24
5.19
4.58
4.53
3.47
1.53
1.51
1.36
1.29
7.12
2.18
1.17
1.03
2.04
1.01
1.00
1.02
1.00
1.03
1.00
3.09
3.00
3.05
ppm

14.1
26.3
27.6
45.5
75.0
78.8
107.2
111.5
117.2
122.2
123.2
125.0
125.2
126.9
127.2
128.1
128.8
130.2
131.0
136.0
136.3
139.3
140.2
154.9
178.6
0
20
40
60
80
100
120
140
160
180
200
220
ppm

1-benzyl-2-oxo-3-vinylindolin-3-yl acrylate (5.3ai)



To an oven-dried round-bottomed flask equipped with a magnetic stir bar was added a solution of 1-benzyl-3-hydroxy-3-vinylindolin-2-one **5.3a** (306 mg, 1.15 mmol, 100 mol%) in 14.0 mL of THF. The solution was treated with NaH 60% dispersion in mineral oil (91.9 mg, 3.82 mmol, 333 mol%) and the resulting suspension was stirred at room temperature for 15 mins. The solution was cooled to 0°C and acryloyl chloride (0.12 mL, 1.50 mmol, 130 mol%) was slowly added at 0°C. The reaction was removed from the ice-bath and was allowed to warm up to ambient temperature and stir for 1 hr. Distilled water was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (1 x 50 mL) and dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to afford the title compound **5.3ai** (344 mg, 1.08 mmol) in 94% yield as a yellow oil.

TLC (SiO_2): R_f= 0.40 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.32 (m, 4H), 7.31 – 7.18 (m, 3H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 1H), 6.46 (d, *J* = 18.3 Hz 1H), 6.18 (ddd, *J* = 19.8, 17.2, 10.5 Hz, 2H), 5.90 (dd, *J* = 10.5, 1.3 Hz, 1H), 5.42 (d, *J* = 10.5 Hz, 1H), 5.33 (d, *J* = 17.2 Hz, 1H), 5.02 (d, *J* = 16.0 Hz, 1H), 4.95 (d, *J* = 16.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 163.9, 143.1, 135.6, 133.5, 132.5, 130.0, 128.8, 127.6, 127.3, 127.1, 126.3, 123.8, 122.9, 119.0, 109.8, 80.7, 44.1.

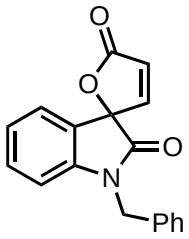
LRMS (ESI): Calcd. for $C_{20}H_{17}NO_3$ $[M+Na]^+$: 342, Found: 342.

FTIR (neat): 3062, 1722, 1613, 1487, 1351, 1176, 979 cm^{-1}.

7.39
7.37
7.36
7.34
7.32
7.29
7.27
7.26
7.24
7.22
7.20
7.07
7.05
6.72
6.70
6.48
6.44
6.24
6.21
6.20
6.19
6.17
6.16
6.15
6.12
5.91
5.91
5.88
5.88
5.43
5.40
5.35
5.31
5.04
5.00
4.97
4.93
4.10
3.00
0.91
0.96
1.01
2.08
1.01
1.05
1.00
1.09
1.06
ppm

44.1
80.7
109.8
119.0
122.9
123.8
126.3
127.1
127.3
127.6
128.8
130.0
132.5
133.5
135.6
143.1
163.9
173.2
0
20
40
60
80
100
120
140
160
180
200
220
ppm

1'-benzyl-5*H*-spiro[furan-2,3'-indoline]-2',5-dione (5.3o)



To an oven-dried round-bottomed flask under an argon atmosphere equipped with a reflux condenser and magnetic stir bar was added 1-benzyl-2-oxo-3-vinylindolin-3-yl acrylate **5.3ai** (184 mg, 0.576 mmol, 100 mol%) in 10.0 mL of toluene. A solution of Grubbs second generation catalyst [$Cl_2(PCy_3)(IMes)Ru{=}CHPh$] (25 mg, 0.0288 mmol, 5 mol%) in 7 mL of toluene was added dropwise using a syringe pump over 1 h at 110°C. After stirring at 110°C for 48 h the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 85:15) to afford the title compound **5.3o** (105 mg, 0.363 mmol) as a tannish solid in 63% yield.

TLC (SiO_2): R_f= 0.40 (hexanes:ethyl acetate = 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.23 (m, 7H), 7.14 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.08 (td, *J* = 7.5, 1.0 Hz, 1H), 6.83 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.46 (d, *J* = 5.5 Hz, 1H), 4.96 (d, *J* = 15.7 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H).

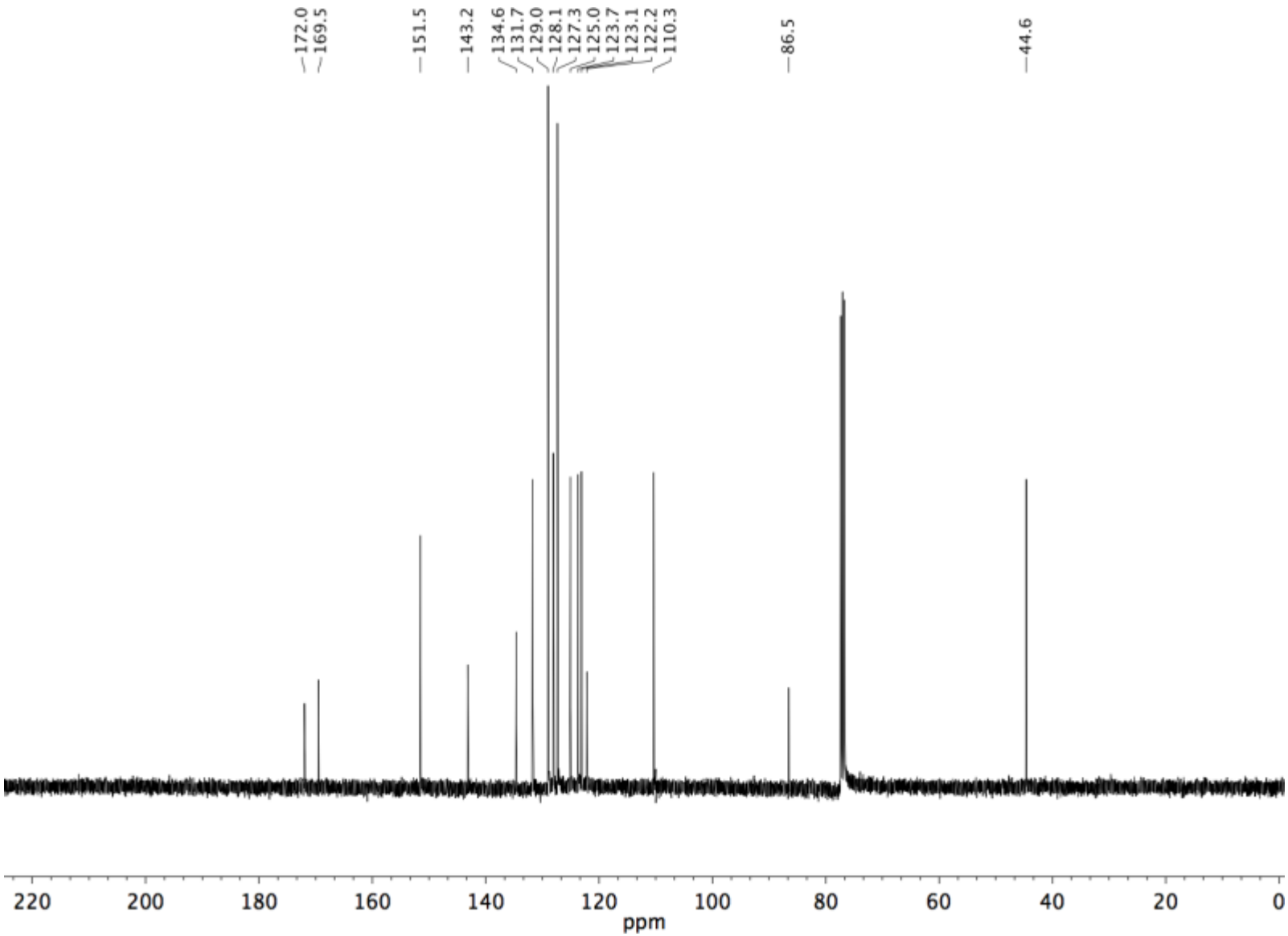
^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 169.5, 151.5, 143.2, 134.6, 131.7, 129.0, 128.1, 127.3, 125.0, 123.7, 123.1, 122.2, 110.3, 86.5, 44.6.

M.P. 158-159 °C

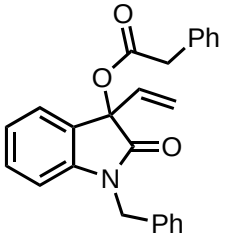
LRMS (ESI): Calcd. for $C_{18}H_{13}NO_3$ $[M+Na]^+$: 314, Found: 314.

FTIR (neat): 3689, 3091, 1758, 1718, 1615, 1488, 992 cm^{-1}.

7.37
7.35
7.33
7.32
7.30
7.28
7.26
7.16
7.15
7.14
7.13
7.10
7.10
7.08
7.08
7.06
7.06
6.84
6.82
6.47
6.45
4.98
4.94
4.93
4.89
7.20
1.06
1.08
1.07
1.00
1.07
1.07
ppm
0
1
2
3
4
5
6
7
8
9
10


172.0
169.5
151.5
143.2
134.6
131.7
129.0
128.1
127.3
125.0
123.7
123.1
122.2
110.3
86.5
44.6
220
200
180
160
140
120
100
80
60
40
20
0
ppm

1-benzyl-2-oxo-3-vinylindolin-3-yl 2-phenylacetate (5.3aii)



To an oven-dried round-bottom flask equipped with a magnetic stir bar was added a solution of 1-benzyl-3-hydroxy-3-vinylindolin-2-one **5.3a** (306 mg, 1.15 mmol, 100 mol%) in 14.0 mL of THF. The solution was treated with NaH 60% dispersion in mineral oil (91.9 mg, 3.82 mmol, 333 mol%) and the resulting suspension was stirred at room temperature for 15 mins. The solution was cooled to 0°C and phenylacetyl chloride (0.18 mL, 1.38 mmol, 120 mol%) was slowly added at 0°C. The reaction was removed from the ice-bath and was allowed to warm up to ambient temperature and stir for 1 hr. Distilled water was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (1 x 50 mL) and dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to afford the title compound **5.3aii** (422 mg, 1.10 mmol) as a yellow oil in 96% yield.

TLC (SiO_2): R_f= 0.40 (hexanes:ethyl acetate = 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.26 (m, 10H), 7.20 (td, *J* = 7.7, 1.4 Hz, 1H), 7.10 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.11 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.40 (dd, *J* = 10.5, 0.6 Hz, 1H), 5.30 (dd, *J* = 17.1, 0.6 Hz, 1H), 5.04 (d, *J* = 16.0 Hz, 1H), 4.90 (d, *J* = 16.0 Hz, 1H), 3.76 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 169.3, 143.1, 135.6, 133.4, 133.3, 129.9, 129.3, 128.8, 128.6, 127.6, 127.2, 127.1, 127.1, 126.3, 123.6, 122.9, 118.9, 109.8, 80.9, 44.1, 40.9.

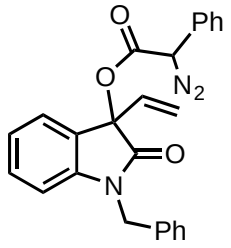
LRMS (ESI): Calcd. for $C_{25}H_{21}NO_3$ $[M+Na]^+$: 406, Found: 406.

FTIR (neat): 3029, 2923, 1727, 1613, 1487, 1481, 981 cm^{-1}.

7.38
7.36
7.34
7.33
7.31
7.30
7.28
7.26
7.22
7.22
7.20
7.20
7.18
7.18
7.11
7.11
7.09
7.09
7.03
7.03
7.01
7.01
6.70
6.68
6.15
6.12
6.11
6.08
5.41
5.41
5.38
5.38
5.32
5.32
5.28
5.28
5.06
5.02
4.92
4.88
3.76
10.14
1.05
1.00
1.00
1.00
1.02
0.98
1.03
1.02
1.03
1.03
2.00
ppm

173.2
169.3
143.1
135.6
133.4
133.3
129.9
129.3
128.8
128.6
127.6
127.2
127.1
127.1
126.3
123.6
122.9
118.9
109.8
80.9
44.1
40.9
0
20
40
60
80
100
120
140
160
180
200
220
ppm

1-benzyl-2-oxo-3-vinylindolin-3-yl 2-diazo-2-phenylacetate (5.3aiii)



To an oven-dried round-bottom flask equipped with a magnetic stir bar was added a solution of 1-benzyl-2-oxo-3-vinylindolin-3-yl 2-phenylacetate **5.3aii** (328 mg, 0.855 mmol, 100 mol%) in 2.6 mL of THF. The reaction was cooled to 0°C and *p*-ABSA (246 mg, 1.03 mmol, 120 mol%) and DBU (0.2 mL, 1.28 mmol, 150 mol%) were added slowly at 0°C. The reaction was removed from the ice-bath and was allowed to warm up to ambient temperature and stir for 1 hr. Ammonium chloride (sat.) (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were washed with brine (1 x 50 mL) and dried over $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: hexanes:ethyl acetate = 8:2) to afford the title compound **5.3aiii** (323 mg, 0.786 mmol) as a yellow oil in 92% yield.

TLC (SiO_2): R_f= 0.30 (hexanes:ethyl acetate = 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.27 (m, 10H), 7.23 (td, *J* = 7.8, 1.3 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.12 (dd, *J* = 17.1, 10.5 Hz, 1H), 5.42 (dd, *J* = 10.5, 0.6 Hz, 1H), 5.31 (dd, *J* = 17.1, 0.6 Hz, 1H), 5.09 (d, *J* = 15.9 Hz, 1H), 4.92 (d, *J* = 15.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 162.7, 143.0, 135.6, 133.3, 130.1, 128.9, 128.8, 127.6, 127.2, 126.5, 126.1, 124.8, 124.2, 123.9, 123.0, 119.0, 109.9, 81.0, 44.2.

LRMS (ESI): Calcd. for $C_{25}H_{19}N_3O_3$ $[M+Na]^+$: 432, Found: 432.

FTIR (neat): 3126, 2920, 2109, 1742, 1693, 1573, 995 cm^{-1}.

7.43
7.43
7.41
7.41
7.39
7.38
7.37
7.37
7.35
7.35
7.33
7.33
7.31
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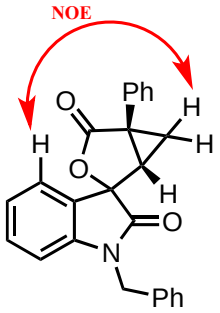
7.28
7.24
7.23
7.18
7.08
7.07
7.06
6.74
6.15
6.13
6.11
6.09
5.43
5.41
5.41
5.33
5.33
5.29
5.29
5.11
5.07
4.94
4.90
10.24
1.19
1.13
1.02
0.96
0.95
0.96
0.96
0.94
1.00
ppm
0
1
2
3
4
5
6
7
8
9
10

44.2
81.0
109.9
119.0
123.0
123.9
124.2
124.8
126.1
126.5
127.2
127.6
128.8
128.9
130.1
133.3
135.6
143.0
162.7
173.3
0
20
40
60
80
100
120
140
160
180
200
220
ppm

(1S,5R)-1'-benzyl-5-phenyl-3-oxaspiro[bicyclo[3.1.0]hexane-2,3'-indoline]-2',4-dione (5.3p)



To a resealable pressure tube (13 x 100 mm) equipped with a magnetic stir bar was added $Rh_2(OAc)_4$ (0.66 mg, 0.0015 mmol, 1 mol%) in 1.5 mL of CH_2Cl_2. 1-Benzyl-2-oxo-3-vinylindolin-3-yl 2-diazo-2-phenylacetate **5.3aiii** (61.5 mg, 0.15 mmol, 100 mol%) in 1.5 mL of THF was added dropwise using a syringe pump over 2 h at ambient temperature. After stirring at ambient temperature for 20 h, the reaction mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2: 15% ethyl acetate in hexanes) to afford the title compound **5.3p** (35 mg, 0.092 mmol) as a yellow oil in 61% yield in a 10:1 diastereomeric ratio.

TLC (SiO_2): R_f= 0.40 (hexanes:ethyl acetate = 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 7.64 (m, 2H), 7.48 – 7.44 (m, 1H), 7.42 – 7.39 (m, 2H), 7.38 – 7.29 (m, 7H), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 4.95 (s, 2H), 2.49 (dd, *J* = 7.8, 4.6 Hz, 1H), 1.88 (dd, *J* = 5.4, 4.6 Hz, 1H), 1.76 (dd, *J* = 7.8, 5.4 Hz, 1H).

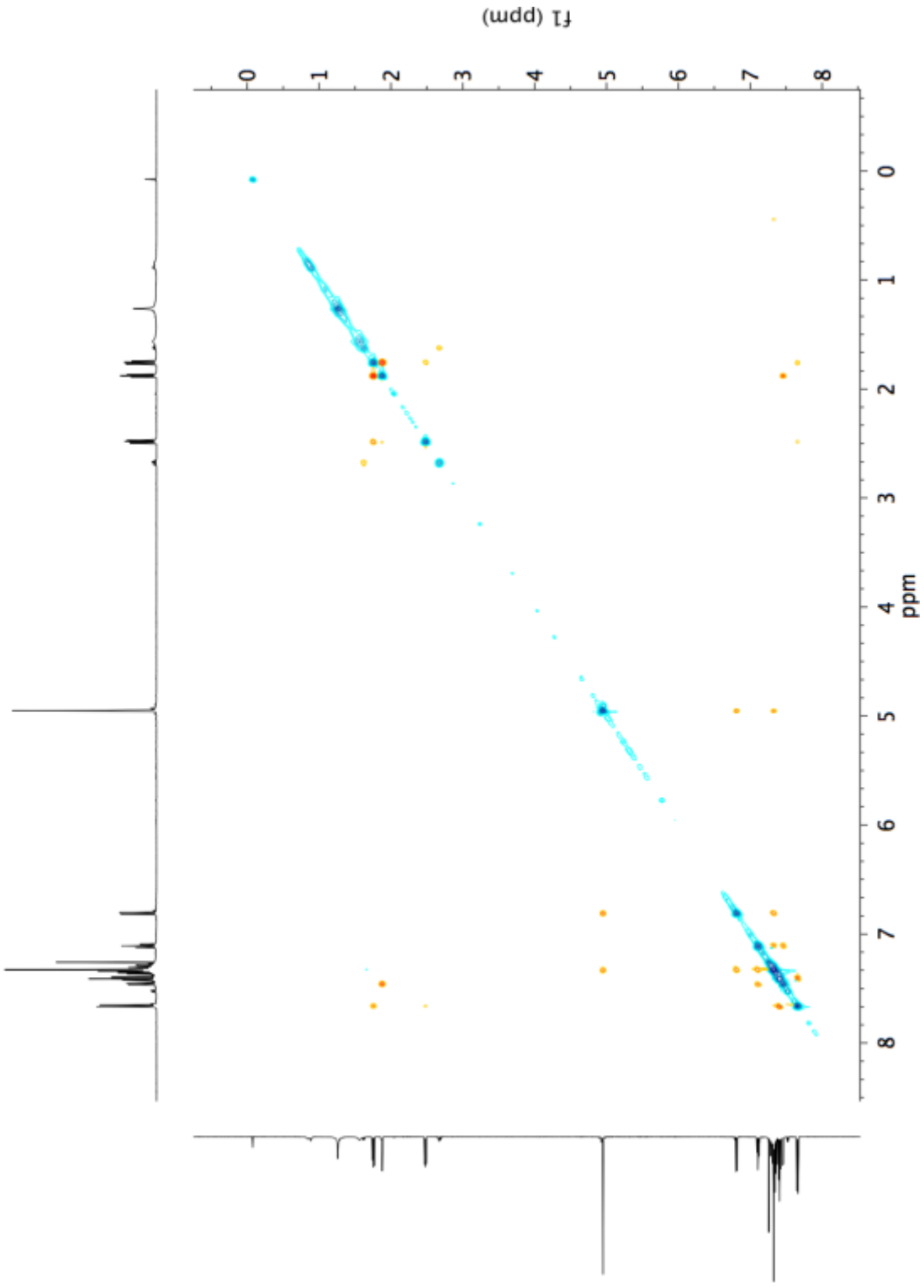
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 173.7, 143.3, 134.9, 132.8, 131.3, 129.8, 129.0, 128.7, 128.3, 128.2, 128.0, 127.3, 124.6, 124.3, 123.5, 110.1, 79.9, 44.1, 33.2, 31.0, 14.4.

LRMS (ESI): Calcd. for $C_{25}H_{19}NO_3$ $[M+Na]^+$: 404, Found: 404.

FTIR (neat): 3061, 2925, 1783, 1724, 1614, 1467, 986 cm^{-1}.

7.67
7.67
7.66
7.65
7.65
7.47
7.47
7.47
7.45
7.45
7.44
7.43
7.43
7.41
7.41
7.40
7.40
7.37
7.36
7.35
7.33
7.31
7.31
7.29
7.26
7.13
7.13
7.11
7.11
7.09
7.09
6.82
6.80
4.95
2.50
2.49
2.48
2.47
1.90
1.88
1.88
1.87
1.78
1.77
1.76
1.75
1.97
1.13
2.31
7.25
1.16
1.01
2.00
0.95
1.03
1.02
ppm

14.4
31.0
33.2
44.1
79.9
110.1
123.5
124.3
124.6
127.3
128.0
128.2
128.3
128.7
129.0
129.8
131.3
132.8
134.9
143.3
173.7
174.8
0
20
40
60
80
100
120
140
160
180
200
220
ppm


f1 (ppm)
ppm

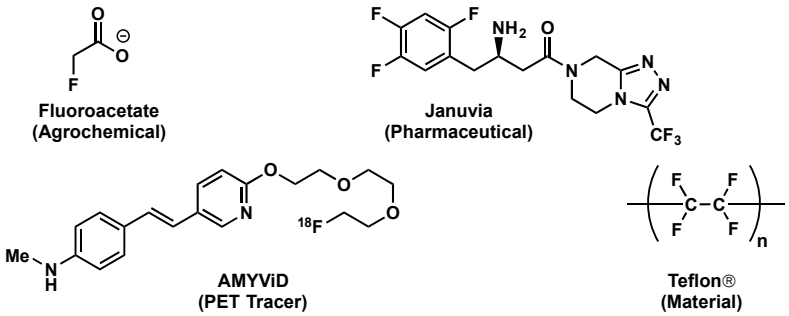
Chapter 6: Transition Metal Catalyzed Couplings of Organofluorine Compounds via Transfer Hydrogenation

6.1 INTRODUCTION

Organofluorine chemistry has caught the attention of many chemical researchers in the areas of organic synthesis. Due to fluorine's unique ability to affect the properties of organic molecules through its strong polar interactions from its intrinsically high electronegativity, size and other attributes have led to the advancements in pharmaceuticals,[88,89] agrochemicals,[90] materials[91] and tracers for positron emission tomography (PET)[92] (**Figure 6.1**). One demonstration of fluorine's impact can be seen in its incorporation into pharmaceuticals which can modulate the acidity, metabolic stability and protein binding affinity of a molecule.[88]

Many methods have been developed for the introduction of fluorine and fluorine containing functional groups.[93–95] Despite these advances there is a paucity of methods for the formation new carbon-carbon bonds using fluorinated carbon sources, such as the addition of non-stabilized carbon nucleophiles to fluorinated aldehydes.[96,97] Certain metal catalysts have shown to promote C-C couplings of π-unsaturated couplings *via* transfer hydrogenation[83] and with this technology thus leading to more efforts in expanding this field.

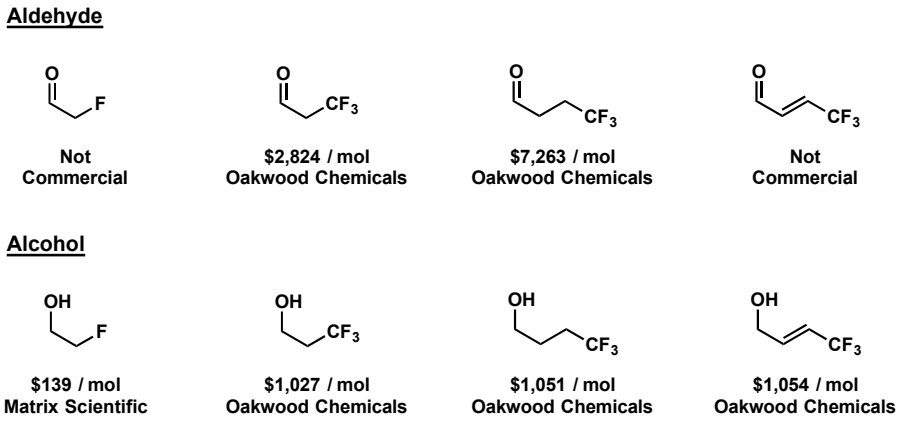
Figure 6.1: Selected examples of organofluorine compounds



6.2 BACKGROUND

Only few studies of addition of non-stabilized carbon nucleophiles to fluorinated aldehydes exist.[96,97] Reports of metal catalyzed additions of carbon nucleophiles to fluorinated aldehydes are limited to carbonyl-ene, Mukaiyama aldol and Friedel-Crafts reactions.[98] This limitation is a manifestation of the intractability and propensity of fluorinated aldehydes undergoing self-condensation or reduction upon exposure to main group organometallics such as Grignard reagents.[96,97] In contrast, fluorinated alcohol equivalents are stable, abundant and relatively inexpensive to their carbonyl counterparts (**Figure 6.2**).[99]

Figure 6.2: Prices for selected fluorinated aldehydes and alcohol congeners

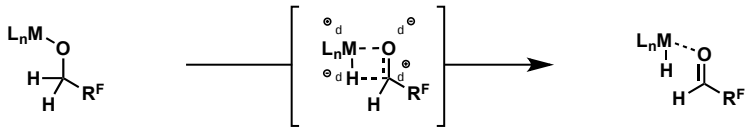


Under metal catalyzed transfer hydrogenative carbonyl addition conditions, alcohols are able to serve as the synthetic equivalents to their carbonyl congeners thus enabling additions that would otherwise be unobtainable or problematic due to traditional carbonyl addition chemistry of the reactive fluorinated aldehyde compounds. For example, 1,3-dialdehydes are relatively unstable, but in contrast 1,3-diols can be used in catalytic enantioselective double allylation or crotylation *via* redox-triggered carbonyl addition.[100] This redox-triggered process has a molecule of hydrogen transfer from the alcohol to the π-unsaturate to generate a transient carbonyl-organometal pair that can then

undergo carbonyl addition.[83] The generation of catalytic amounts of the transient aldehyde might help mitigate decomposition of highly reactive aldehydes.

To test the feasibility of engaging fluorinated alcohols in redox-triggered carbonyl addition was met with three possible setback: (1) the relatively high strength of the carbinol C-H bonds in fluorinated alcohols, (2) the increased endothermicity of dehydrogenation, which being reversible would shorten the lifetime of the transient aldehyde[101] and (3) the large destabilizing effect of fluoroalkyl groups in regards to the transition state for the β-hydride elimination (up to 15 kcal/mol) (**Scheme 6.1**).[101]

Scheme 6.1: Inductive fluoroalkyl moieties and its effect on β-hydride elimination

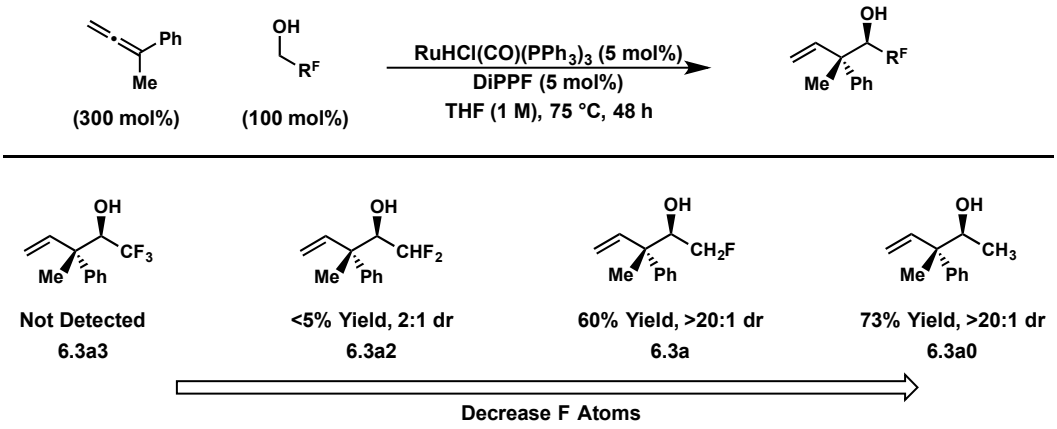


6.3 REACTION DEVELOPMENT

In initial experiments to test the effects of the number of fluorine atom and how this would affect the proposed reactivity. Mono-, di-, and tri- fluoro ethanol and ethanol were treated with 1-methyl-1-phenylallene under the previously established conditions for the coupling of non-fluorinated primary alcohols to 1,1-disubstituted allenes (**Figure 6.3**).[102] Exposure of the fluorinated alcohols with a ruthenium(II) catalyst modified by DiPPF showed that trifluoroethanol displayed no reactivity giving no trace of product **6.3a3**. By removing one atom of fluorine, the desired coupling product **6.3a2** was obtained in less than 5% yield with 2:1 diastereoselectivity. Removing an additional fluorine atom lead to the formation of coupling product **6.3a** in 60% yield with excellent selectivity. Lastly with ethanol as the alcohol coupling partner the observed coupling product was obtained as reported in previous work.[102] These results would indicate that

the limit of dehydrogenation of fluorinated alcohols is the mono-fluoroethanol. It is to be noted that an extensive effort was conducted to improve conversion for coupling products **6.3a3** and **6.3a2** through ligand, metal and other parameters, but no improvements were observed.

Figure 6.3: Initial probe of the limits of fluorinated alcohols

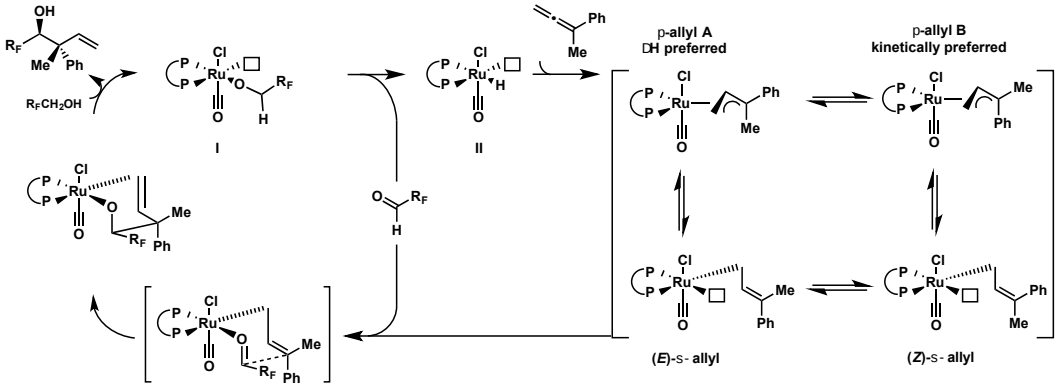


6.4 PROPOSED MECHANISM

Based on related ruthenium catalyzed allene-aldehyde couplings, a hydrometallative pathway is postulated to occur (**Figure 6.4**).[83,102] The catalytic cycle begins with hydrometallation of the allene to form the π-allylruthenium intermediate, evidence of such process has been reported prior.[103–105] Hydrometallation from the allene π-face proximal to the smaller methyl group is anticipated to be the kinetically favored. Rapid isomerization then occurs from π-allyl complex **B** to the more stable π-allyl complex **A**.[102,103,106,107] Carbonyl addition then occurs by way of the (*E*)-σ-allyl haptomer *via* a closed six-membered chair-like transition state forming the *anti*–diastereomer. Proton exchange of the ruthenium alkoxide by another molecule of alcohol releases the fluorinated adduct and ruthenium alkoxide **I**. Then upon dehydrogenation of **I** releases

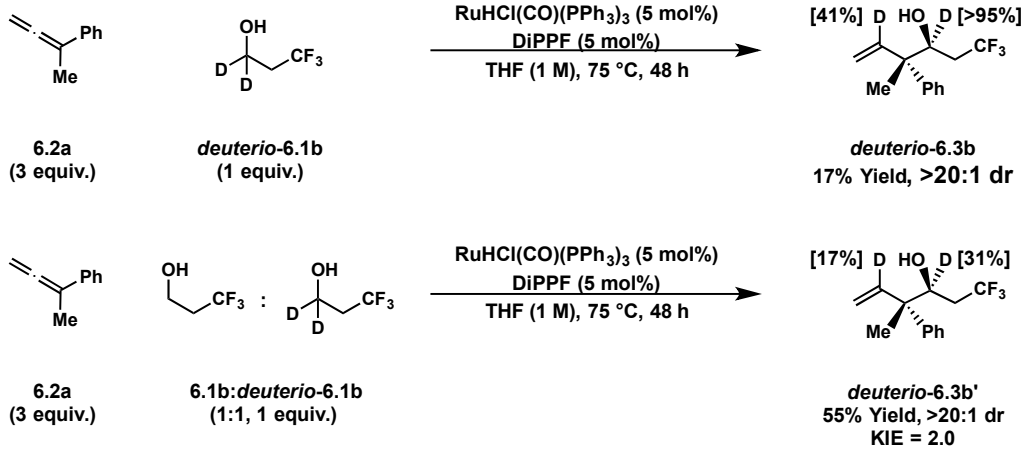
another molecule of aldehyde and regenerates the ruthenium hydride complex **II** to close the catalytic cycle.

Figure 6.4: Proposed mechanism of fluorinated alcohol coupling with allenes



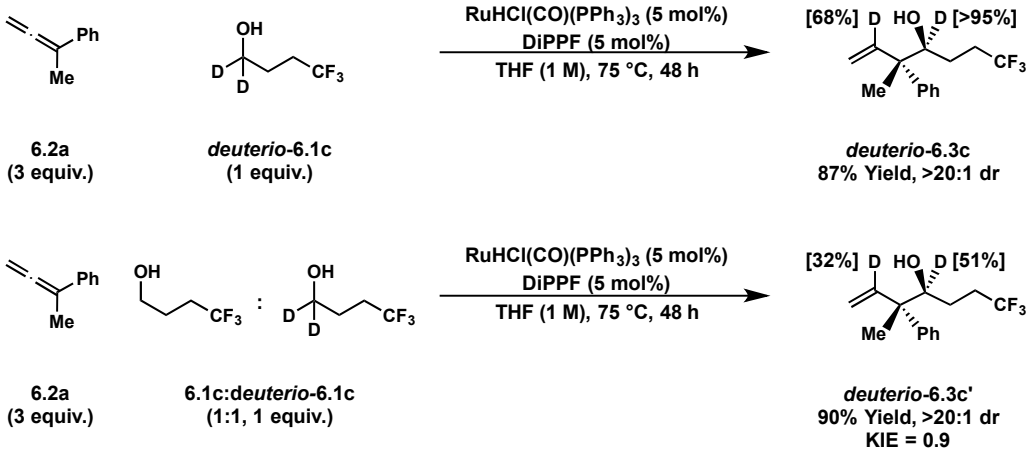
A set of competition kinetic experiments were conducted, by way of deuterium labeling experiments, to corroborate the anticipated effects of fluorine on the β-hydride elimination event.[99] In the first experiment where *deuterio*-3,3,3-trifluoropropanol ***deuterio*-6.1b** is coupled with 1-methyl-1-phenylallene **6.2a** furnished ***deuterio*-6.3b** in 17% yield (**Scheme 6.2**). Deuterium is completely retained at the carbinol position ***deuterio*-6.3b**, suggesting that the secondary alcohol product is inert with respect to dehydrogenation. Incomplete deuterium incorporation at the interior vinylic position of ***deuterio*-6.3b** (41% ^{2}H) may be due to β-hydride elimination of the allylruthenium intermediate which leads to diene byproducts which have been detected by crude NMR and explains the use of excess allene in the reaction. Adventitious water may also diminish the level of deuterium incorporation.[56] The low yields of ***deuterio*-6.3b** compared to the non-deuterated counterpart suggests that the dehydrogenation is turn-over limiting. To test the validity that the dehydrogenation is turn-over limiting, equimolar quantities of **6.1b** and ***deuterio*-6.1b** were subjected to the reaction condition and a primary kinetic isotope effect of 2.0 is observed.

Scheme 6.2: Competition kinetics studies with *deuterio*-3,3,3-trifluoropropanol



In contrast with the second set of experiments (**Scheme 6.3**) where *deuterio*-4,4,4-trifluorobutanol ***deuterio*-6.1c** where the trifluoro moiety is even further from the carbinol C-H involved with the dehydrogenation, the observed kinetic isotope effect is 0.9. This result would lead one to believe that *deuterio*-4,4,4-trifluorobutanol ***deuterio*-6.1c'**, β-hydride elimination is not turn-over limiting and that an inverse secondary isotope effect is at play, suggesting that carbonyl addition may be the turn-over limiting step.

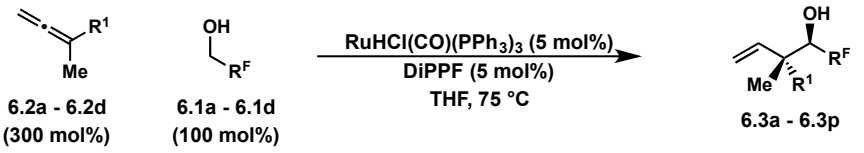
Scheme 6.3: Competition kinetics studies with *deuterio*-4,4,4-trifluorobutanol



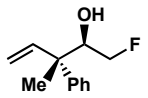
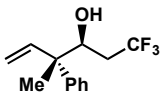
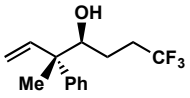
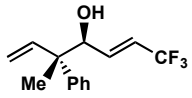
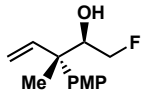
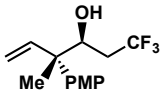
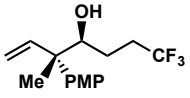
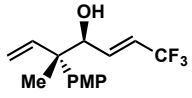
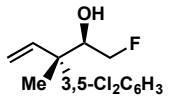
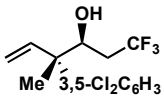
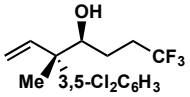
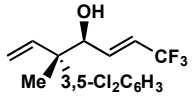
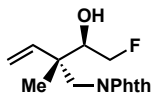
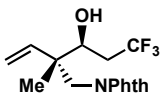
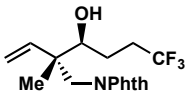
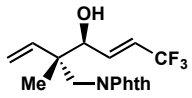
6.5 REACTION SCOPE

To examine the scope of the reaction, fluorinated alcohols **6.1a-6.1d** were coupled with 1,1-disubstituted allenes **6.2a-6.2d** (**Table 6.1**). 1-Metyl-1-arylallenes having electron-donating as well as electron-withdrawing characteristics performed smoothly and delivered the desired coupling products in good yields and excellent selectivity for the *anti*-diastereomer. The use of 1-methyl-1-phthalimidomethyl **6.2b** a dialkyl allene also proceeded and delivered the coupling products albeit selectivity for the *anti*-diastereomer is reduced, but still obtained in synthetically useful levels.

Table 6.1: Examples of ruthenium catalyzed hydrohydroxyfluoroalkylation

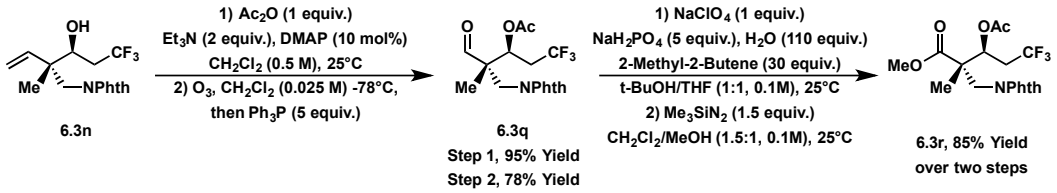


6.2a - 6.2d (300 mol%) | 6.1a - 6.1d (100 mol%) | 6.3a - 6.3p

$R_F = CH_2F$, 6.1a R^1 = Ph, 6.2.a	$R_F = CH_2CF_3$, 6.1b $R^1 = CH_2NPhth$, 6.2b	$R_F = (CH_2)_2CF_3$, 6.1c R^1 = PMP, 6.2c	$R_F = CH{=}CHCF_3$, 6.1d $R^1 = 3,5\text{-}Cl_2C_6H_3$, 6.2d
			
6.3a, 75% Yield, >20:1 dr	6.3b, 77% Yield, >20:1 dr	6.3c, 92% Yield, >20:1 dr	6.3d, 84% Yield, >20:1 dr
			
6.3e, 60% Yield, >20:1 dr	6.3f, 86% Yield, >20:1 dr	6.3g, 8% Yield, >20:1 dr	6.3h, 68% Yield, >20:1 dr
			
6.3i, 65% Yield, >20:1 dr	6.3j, 85% Yield, >20:1 dr	6.3k, 89% Yield, >20:1 dr	6.3l, 80% Yield, >20:1 dr
			
6.3m, 72% Yield, 4:1 dr	6.3n, 65% Yield, 5:1 dr (X-ray)	6.3o, 85% Yield, 5:1 dr	6.3p, 86% Yield, 6:1 dr

The utility of these organofluorine products can be seen by the conversion of adduct **6.3n** to β-amino ester **6.3r** (**Scheme 6.4**). This demonstrates a plausible route to novel trifluoromethyl containing non-proteinogenic amino acids.

Scheme 6.4: Conversion of product **6.3n** to CF_3-containing amino acid



6.6 CONCLUSION

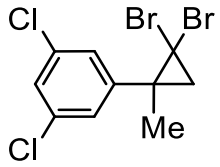
In summary, redox-triggered carbonyl addition catalyzed by a ruthenium catalyst allows the use of fluorinated alcohols to serve as synthetic equivalents to their carbonyl counterpart. This method proceeds by way of transfer hydrogenation and now allows provides a new means of accessing organofluorine compounds. The use of 1,1-disubstituted allenes also allows the formation of all carbon quaternary center with good to excellent levels of diastereoselectivity as well as installing an olefin in the process, providing another point of further functionalization. Future studies will be focused towards the developments of a second-generation catalyst for access to even more highly fluorinate alcohols such as trifluoroethanol and difluoroethanol.

6.7 EXPERIMENTAL SECTION

General Experimental Details. All reactions were run under an atmosphere of argon, unless otherwise indicated. Anhydrous solvents were transferred *via* oven-dried syringes. Reaction tubes and flasks were oven-dried and cooled under a stream of argon. Reaction tubes were purchased from Fischer Scientific (catalog number 14-959-35C). Tetrahydrofuran (THF) was distilled from sodium and benzophenone. $RuHCl(CO)(PPh_3)_3$was prepared according to literature procedure.[108] Fluorinated alcohols were used as received from Matrix Scientific and Oakwood Chemical. Allenes **6.2a**,[109] **6.2b**,[102] and **6.2c**[110] were prepared according to literature procedure. 1,1'-bis(diisopropylphosphino)ferrocene (DiPPF) was obtained from Strem Chemicals Inc and used as received. Analytical thin-layer chromatography (TLC) was carried out using 0.25 mm commercial silica gel plates (Dynamic Adsorbents F254) and products were visualized by UV, $KMnO_4$, and/or Magic Seebach stain. Preparative column chromatography employing Silicycle silica gel (40-63 μm) was performed according to the method of Still.[49] Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. Low-resolution mass spectra (LRMS) and high-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion [M+H]+ or a suitable fragment ion. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, parts per million (ppm) downfield from tetramethylsilane or ppm relative to the center of the singlet at 7.26 ppm for deuterochloroform. Coupling constants are reported in Hertz (Hz). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, ppm relative to the center of the triplet at 77.0 ppm for deuterochloroform. ^{13}C NMR spectra

were routinely run with broadband decoupling. Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Gemini 400 (100 MHz) spectrometer. Deuterium nuclear magnetic resonance (^{2}H NMR) spectra were recorded in $CHCl_3$ solution with a Varian Gemini 500 (77 MHz) spectrometer (relaxation delay 2.00 s).

1,3-dichloro-5-(2,2-dibromo-1-methylcyclopropyl)benzene



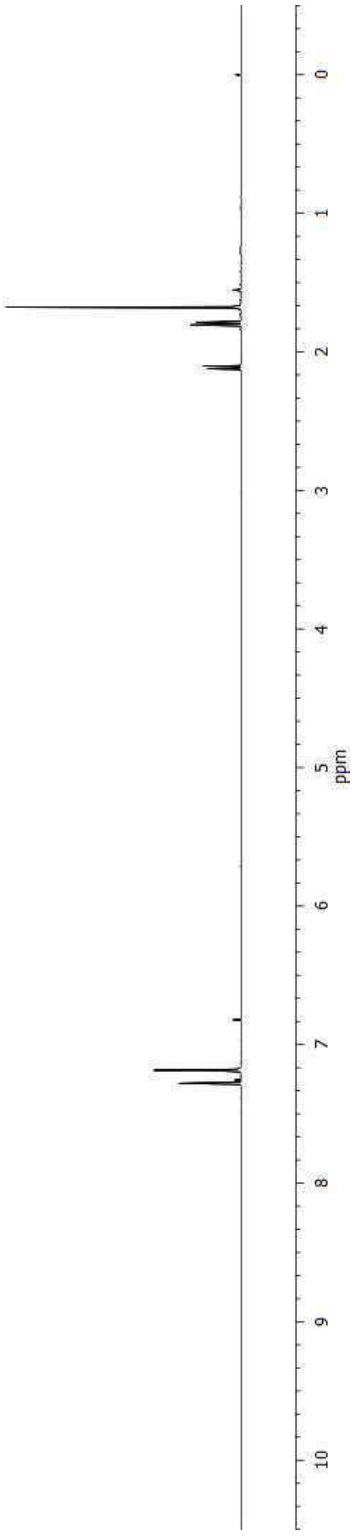
In modification to literature procedure,[111] a flame-dried 50 mL round-bottom flask was charged with 1,3-dichloro-5-(prop-1-en-2-yl)benzene[112] (4.7 g, 25 mmol, 100 mol%), $CHBr_3$ (3.3 mL, 38 mmol, 150 mol%,) and *n*-Bu_4NBr (0.3 g, 1.3 mmol, 5 mol%). To this stirring mixture was dropwise added 50% aqueous NaOH (4.4 mL, 55 mmol, 200 mol%) at ambient temperature. After the addition was complete, the reaction mixture was heated to 50 °C and stirred for 24 hours, then quenched with water (20 mL). The layers were separated, and the aqueous phase was extracted with chloroform (3 × 25 mL). The combined organic phases were successively washed with 1.0 M HCl (2 × 20 mL), water (2 × 20 mL), brine (2 × 20 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 10% EtOAc/hexane) to afford the title compound (4.5 g, 50%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (t, *J* = 1.9 Hz, 1H), 7.18 (d, *J* = 1.9 Hz, 2H), 1.95 (dd, *J* = 126.8, 7.8 Hz, 2H), 1.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 145.5, 134.9, 127.6, 127.2, 35.2, 34.7, 33.8, 27.3.

HRMS (CI) Calcd. For $C_{10}H_8Br_2Cl_2$ $[M]^+$: 355.8366, Found: 355.8366.

FTIR (neat): 2927, 1588, 1561, 1427, 1414, 1384, 1316, 1255, 1134, 1103, 1080, 1062, 1022, 940, 906, 858, 798, 763, 730, 704, 683 cm^{-1}.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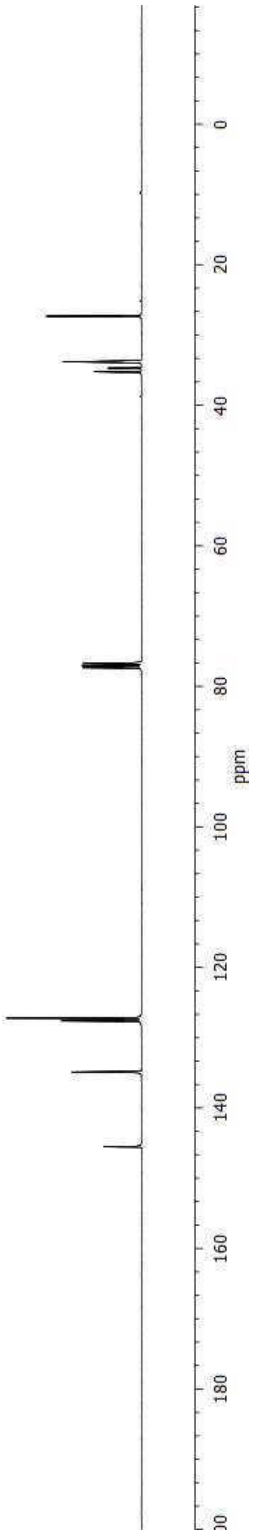
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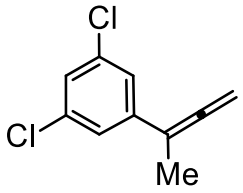
1-(buta-2,3-dien-2-yl)-3,5-dichlorobenzene (6.2d)



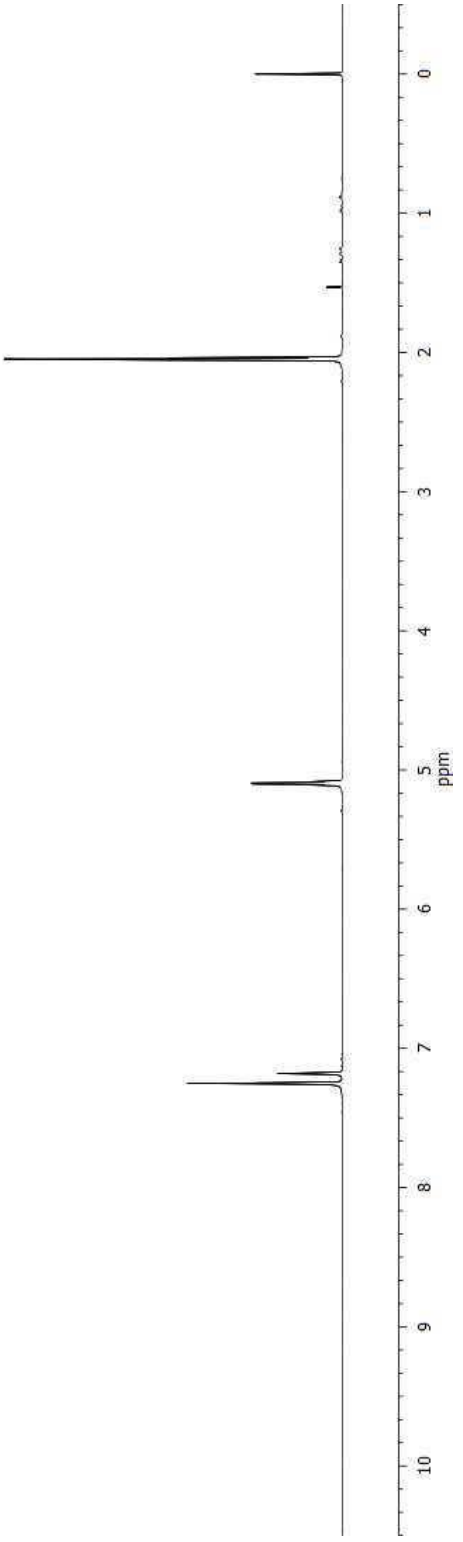
In modification to literature procedure,[113] a flame-dried 50 mL round-bottom flask was charged with dibromocyclopropane (1.4 g, 4 mmol, 100 mol%) and THF (8 mL, 0.5 M). To this stirring mixture was dropwise added 3.0 M ethylmagnesium bromide in THF (2.7 mL, 8 mmol, 200 mol%) at ambient temperature under argon. After stirring for 1 hour, the reaction was quenched with 1.0 M HCl (10 mL). The layers were separated and the aqueous layer was extracted with petroleum ether (2 × 20 mL). The combined organic phases were washed with water (2 × 15 mL), then brine (2 × 15 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was purified by flash column chromatography (SiO_2, 5% EtOAc/hexane) to afford the title compound (318 mg, 40%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.23 (m, 2H), 7.18 (t, J = 1.9 Hz, 1H), 5.10 (q, J = 3.0 Hz, 2H), 2.05 (t, J = 3.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 209.07, 140.24, 134.84, 126.32, 124.05, 98.39, 78.07, 16.37.

HRMS (CI) Calcd. For $C_{10}H_8Cl_2$ $[M]^+$: 198.0080, Found: 198.0080.

FTIR (neat): 1941, 1696, 1583, 1559, 1424, 1407, 1371, 1278, 1255, 1172, 1139, 1099, 952, 905, 852, 796, 729, 686 cm^{-1}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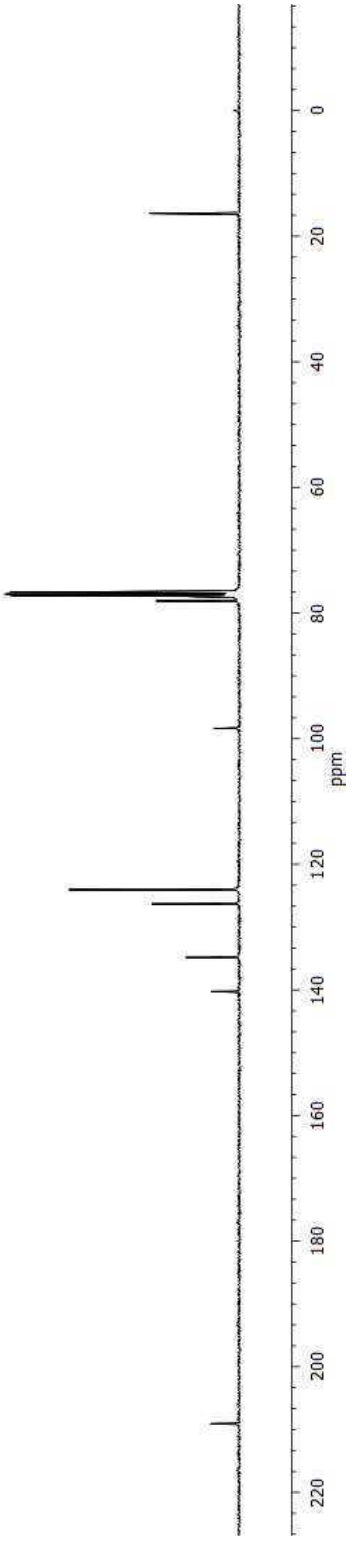
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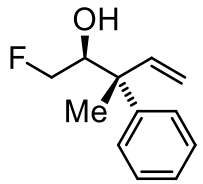
General Procedure A for the coupling of alcohols to allenes

To an oven-dried pressure tube equipped with magnetic stir bar was added RuHCl(CO)(PPh_3)$_3$ (9.5 mg, 0.010 mmol, 5 mol%), 1,1'bis(diisopropylphosphino)ferrocene (DiPPF) (4.2 mg, 0.010 mmol, 5 mol%), and alcohol (0.200 mmol, 100 mol%). The tube was sealed with a rubber septum, purged with argon, and THF (0.05 – 1.0 M with respect to alcohol) and allene (0.600 mmol, 300 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to the indicated temperature for the indicated time. The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2) to furnish the title compounds with yields averaged over two trials.

1-fluoro-3-methyl-3-phenylpent-4-en-2-ol (6.3a)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2a** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 72 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 10% EtOAc/hexane) to furnish the title compound (29.1 mg, 75%, >20:1 *dr*) as a yellow oil.

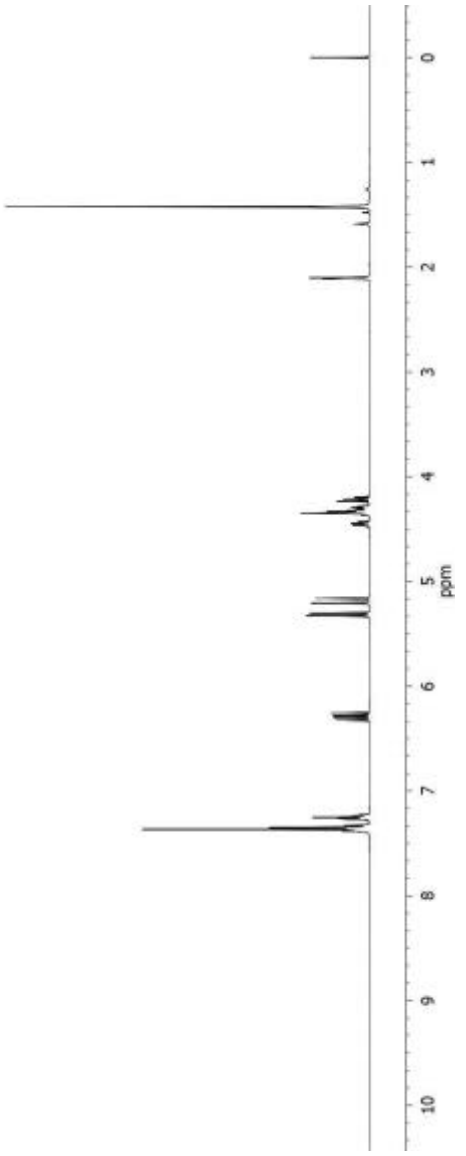
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.31 (m, 4H), 7.31 – 7.19 (m, 1H), 6.29 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.32 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.18 (dd, *J* = 17.7, 1.0 Hz, 1H), 4.51 – 4.15 (m, 3H), 2.11 (d, *J* = 2.9 Hz, 1H), 1.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 142.1, 128.6, 126.8, 126.7, 115.0, 85.0 (d, *J* = 166.4 Hz), 75.7 (d, *J* = 17.7 Hz), 47.5 (d, *J* = 6.9 Hz), 20.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -228.6 – -229.1 (m).

HRMS (CI) Calcd. For $C_{12}H_{15}OF$ $[M]^+$: 194.1107, Found: 194.1107.

FTIR (neat): 3450, 2978, 1637, 1599, 1494, 1446, 1415, 1376, 1289, 1097, 1065, 998, 923, 764, 746, 700 cm^{-1}.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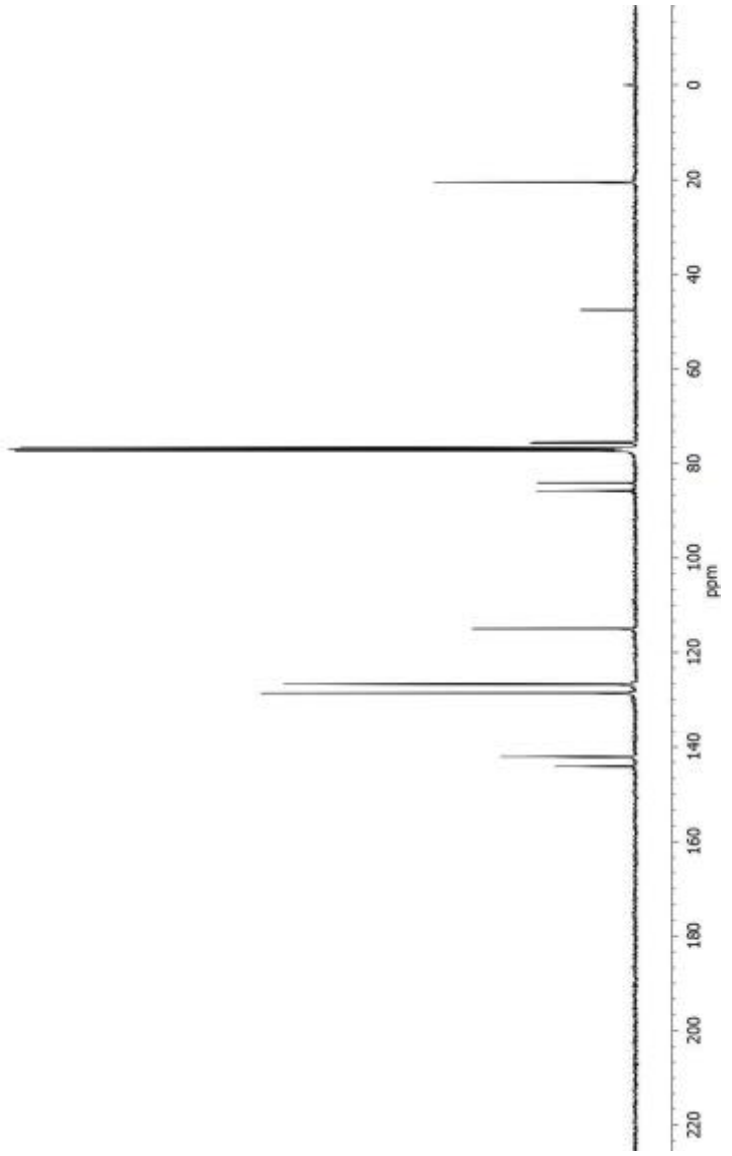
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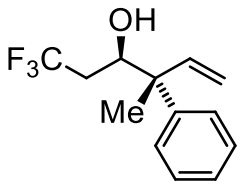
1,1,1-trifluoro-4-methyl-4-phenylhex-5-en-3-ol (6.3b)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2a** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (37.6 mg, 77%, 20:1 *dr*) as a yellow oil.

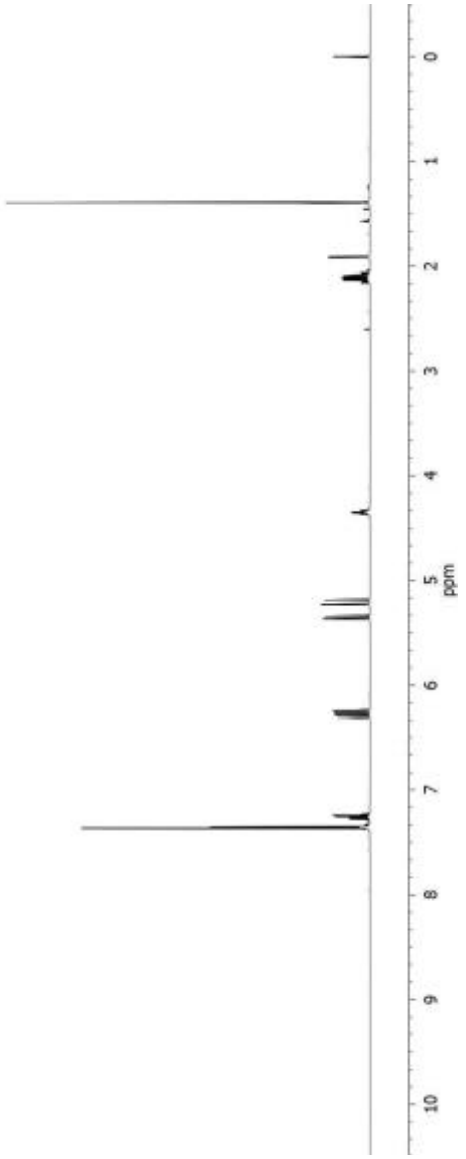
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.29 – 7.22 (m, 1H), 6.28 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.35 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.21 (dd, *J* = 17.7, 1.0 Hz, 1H), 4.40 – 4.30 (m, 1H), 2.20 – 2.04 (m, 2H), 1.91 (dt, *J* = 3.1, 0.8 Hz, 1H), 1.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 141.8, 128.8, 126.9 (q, *J* = 277.0 Hz), 126.9, 126.7, 115.8, 71.5 (d, *J* = 2.5 Hz), 49.3, 36.4 (q, *J* = 27.4 Hz), 19.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.9 (t, *J* = 10.9 Hz).

HRMS (CI) Calcd. For $C_{13}H_{15}OF_3$ $[M]^+$: 244.1075, Found: 244.1074.

FTIR (neat): 3472, 2982, 1638, 1600, 1495, 1446, 1430, 1413, 1378, 1328, 1254, 1119, 1009, 927, 876, 837, 768, 746, 700 cm^{-1}.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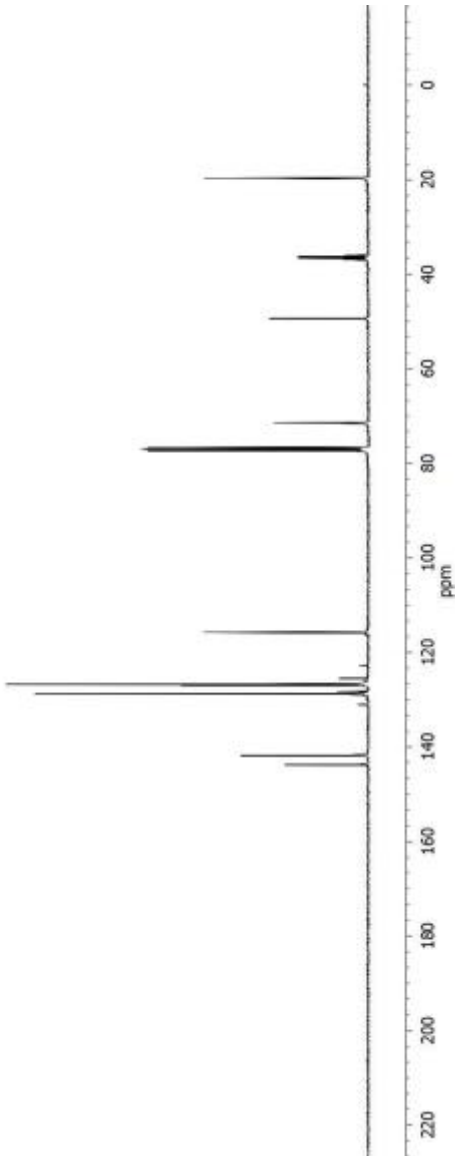
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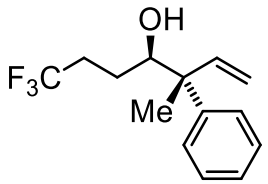
7,7,7-trifluoro-3-methyl-3-phenylhept-1-en-4-ol (6.3c)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2a** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (47.5 mg, 92%, >20:1 *dr*) as a yellow oil.

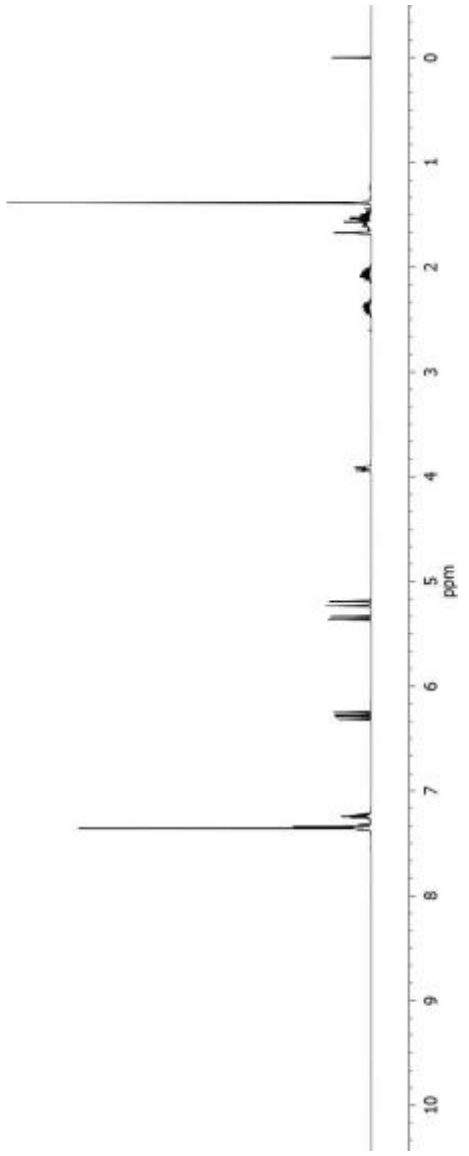
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 4H), 7.28 – 7.21 (m, 1H), 6.28 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.35 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.21 (dd, *J* = 17.7, 1.1 Hz, 1H), 3.93 (dt, *J* = 10.5, 2.8 Hz, 1H), 2.49 – 2.29 (m, 1H), 2.16 – 1.96 (m, 1H), 1.69 – 1.65 (m, 1H), 1.65 – 1.43 (m, 2H), 1.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 142.1, 128.7, 127.4 (q, *J* = 276.3 Hz), 126.7, 126.7, 115.5, 76.1, 49.5, 31.3 (q, *J* = 28.6 Hz), 23.8 (d, *J* = 2.7 Hz), 20.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.3 (t, *J* = 11.1 Hz).

HRMS (CI) Calcd. For $C_{14}H_{16}OF_3$ $[M-H]^+$: 257.1153, Found: 257.1157.

FTIR (neat): 3458, 2983, 1638, 1600, 1494, 1446, 1416, 1376, 1280, 1252, 1224, 1132, 1078, 1047, 1017, 922, 838, 764, 742, 700 cm^{-1}.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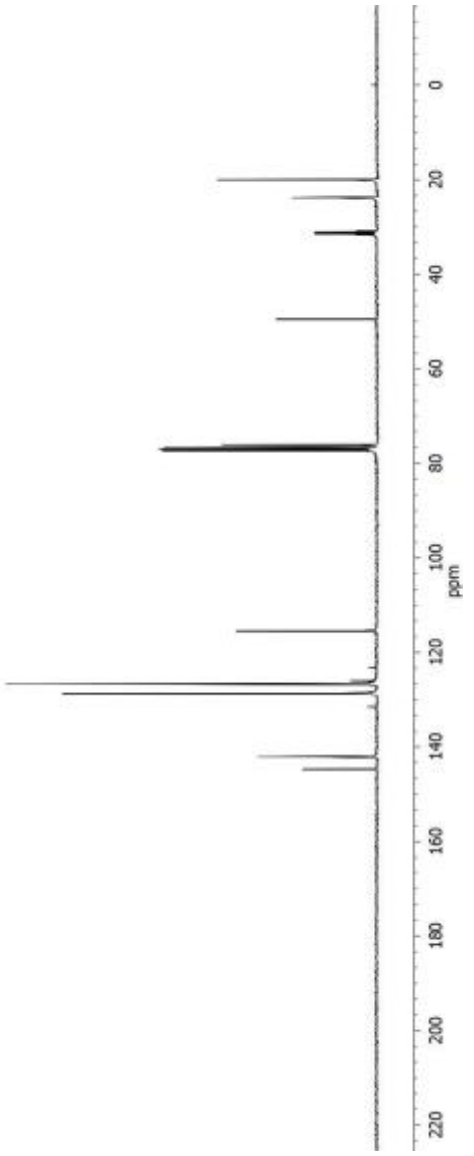
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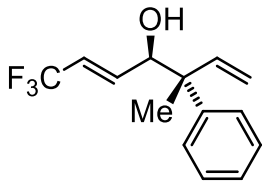
(*E*)-7,7,7-trifluoro-3-methyl-3-phenylhepta-1,5-dien-4-ol (6.3d)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2a** and THF (2.0 mL, 0.1 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (44.6 mg, 87%, >20:1 *dr*) as a yellow oil.

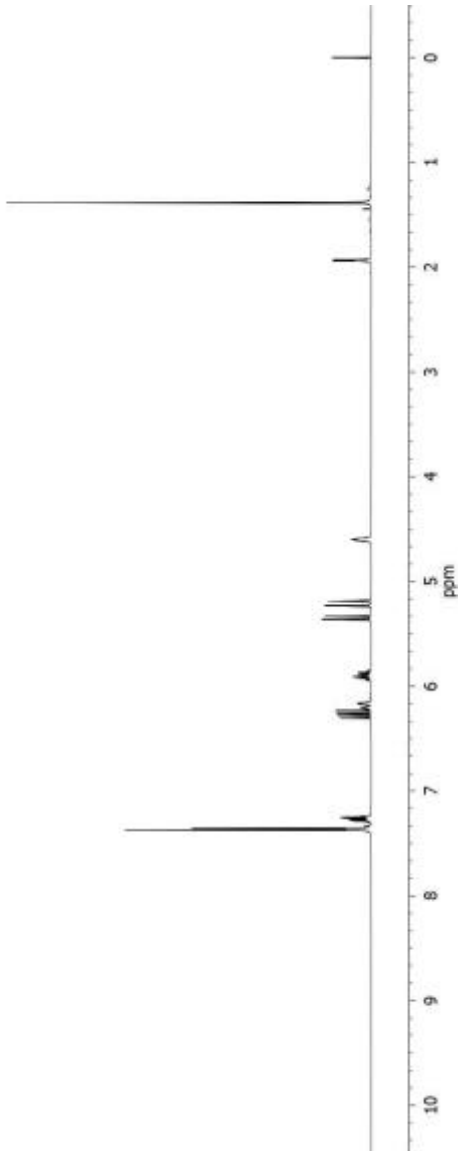
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.33 (m, 4H), 7.30 – 7.23 (m, 1H), 6.27 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.23 – 6.14 (m, 1H), 5.95 – 5.84 (m, 1H), 5.35 (dd, *J* = 10.9, 0.9 Hz, 1H), 5.21 (dd, *J* = 17.6, 0.9 Hz, 1H), 4.64 – 4.57 (m, 1H), 1.95 – 1.91 (m, 1H), 1.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 141.9, 138.1 (q, *J* = 6.3 Hz), 128.7, 127.0, 126.8, 123.1 (q, *J* = 269.3 Hz), 119.9 (q, *J* = 33.8 Hz), 115.9, 75.6, 49.4, 19.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.0 – -64.1 (m).

HRMS (CI) Calcd. For $C_{14}H_{16}OF_3$ $[M+H]^+$: 257.1153, Found: 257.1155.

FTIR (neat): 3461, 2980, 1682, 1638, 1600, 1495, 1446, 1415, 1376, 1308, 1265, 1117, 1095, 1030, 976, 924, 868, 763, 735, 700 cm^{-1}.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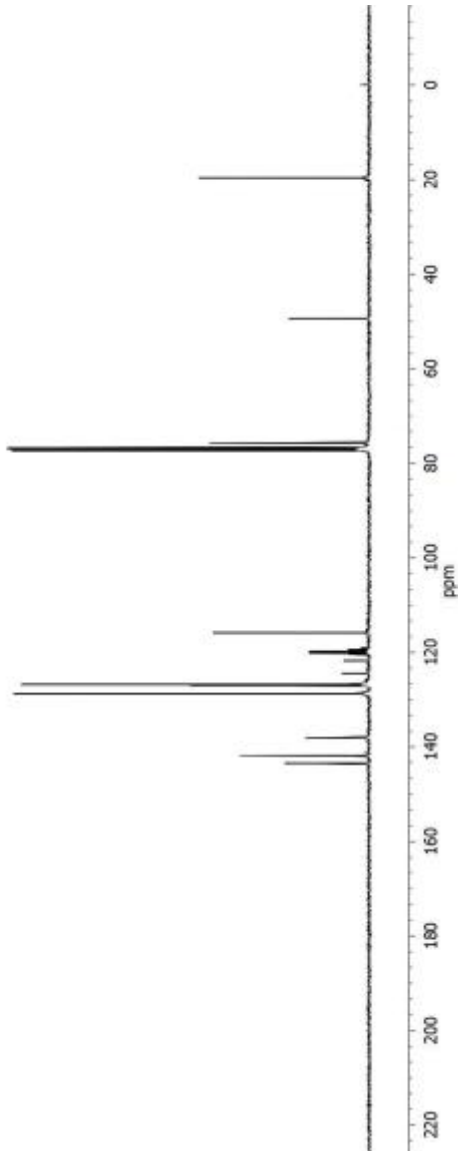
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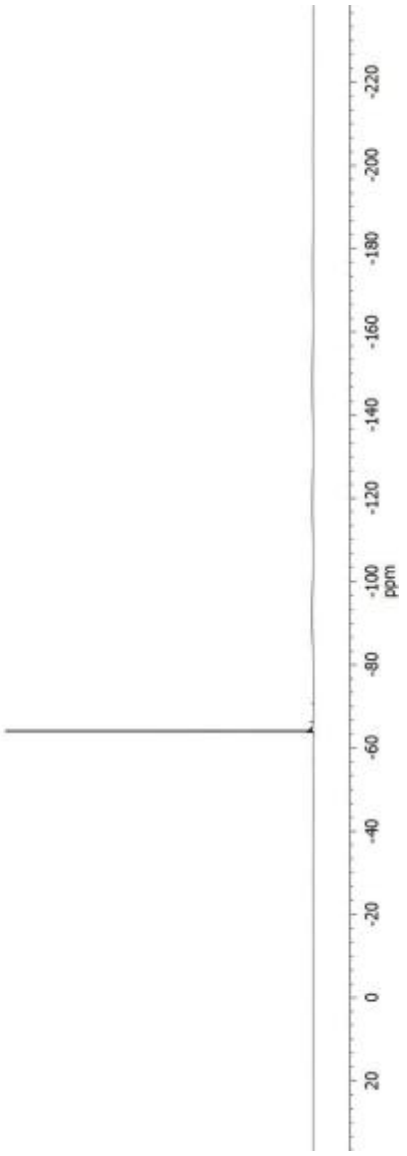
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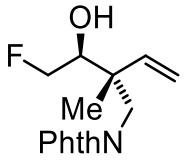
2-(2-(2-fluoro-1-hydroxyethyl)-2-methylbut-3-en-1-yl)isoindoline-1,3-dione (6.3m)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2b** and THF (0.2 mL, 1.0 M with respect to alcohol) at 95 °C for 72 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 20% EtOAc/hexane) to furnish the title compound (32.7 mg, 72%, 4:1 *dr*) as a yellow oil.

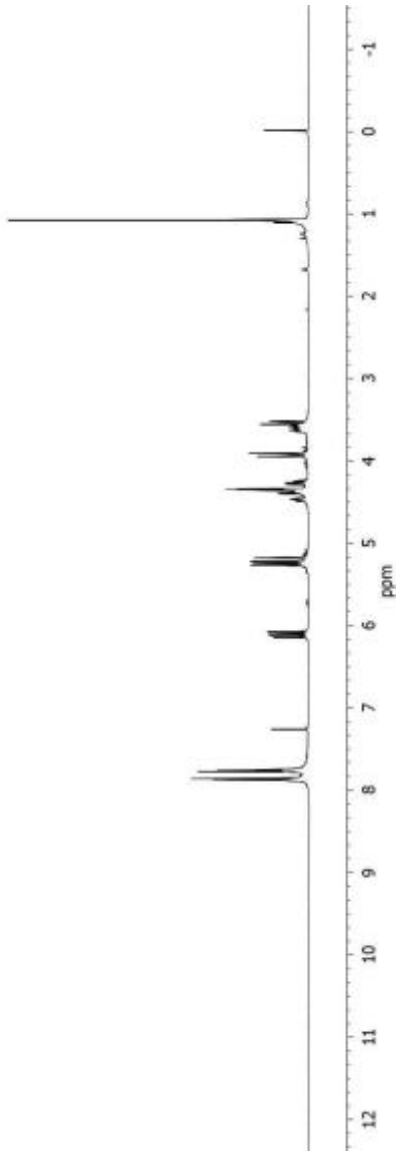
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.76 (dd, *J* = 5.3, 3.1 Hz, 2H), 6.11 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.25 (d, *J* = 10.9 Hz, 1H), 5.20 (d, *J* = 17.8 Hz, 1H), 4.51 – 4.22 (m, 3H), 3.96 – 3.49 (m, 2H), 3.66 – 3.57 (m, 1H), 1.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 138.2, 134.4, 131.6, 123.6, 116.2, 84.4 (d, *J* = 168.6 Hz), 73.1 (d, *J* = 18.4 Hz), 45.3 (d, *J* = 6.4 Hz), 44.6, 18.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ -227.0 (td, *J* = 47.3, 18.0 Hz).

HRMS (CI) Calcd. For $C_{15}H_{17}NO_3F$ $[M+H]^+$: 278.1192, Found: 278.1193.

FTIR (neat): 3477, 2979, 1772, 1701, 1612, 1468, 1435, 1393, 1333, 1190, 1172, 1069, 1000, 916, 796, 754, 716, 667 cm^{-1}.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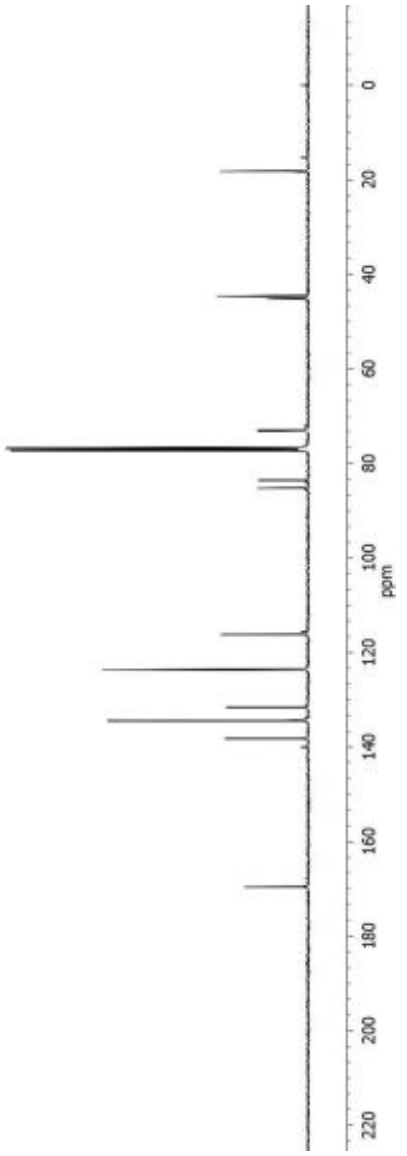
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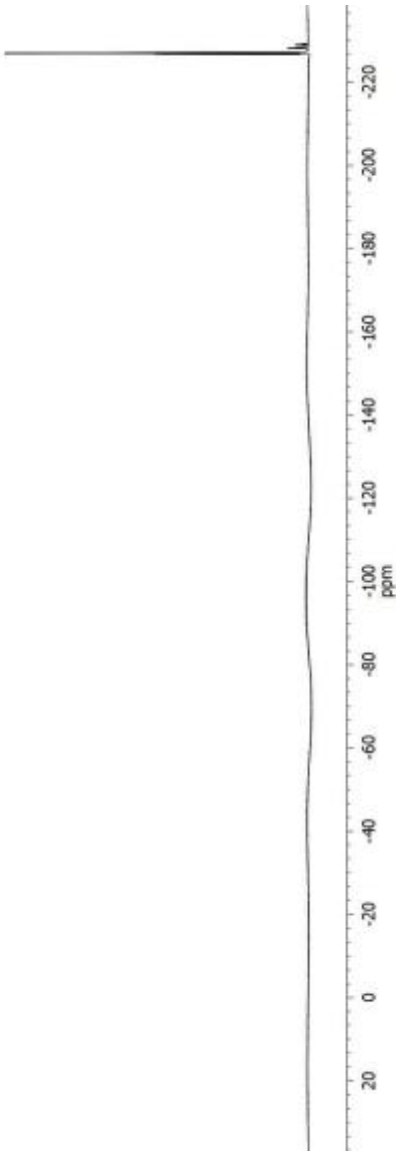
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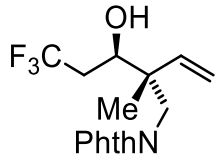
2-(5,5,5-trifluoro-3-hydroxy-2-methyl-2-vinylpentyl)isoindoline-1,3-dione (6.3n)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2b** and THF (0.2 mL, 1.0 M with respect to alcohol) at 95 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (42.5 mg, 65%, 5:1 *dr*) as a yellow oil.

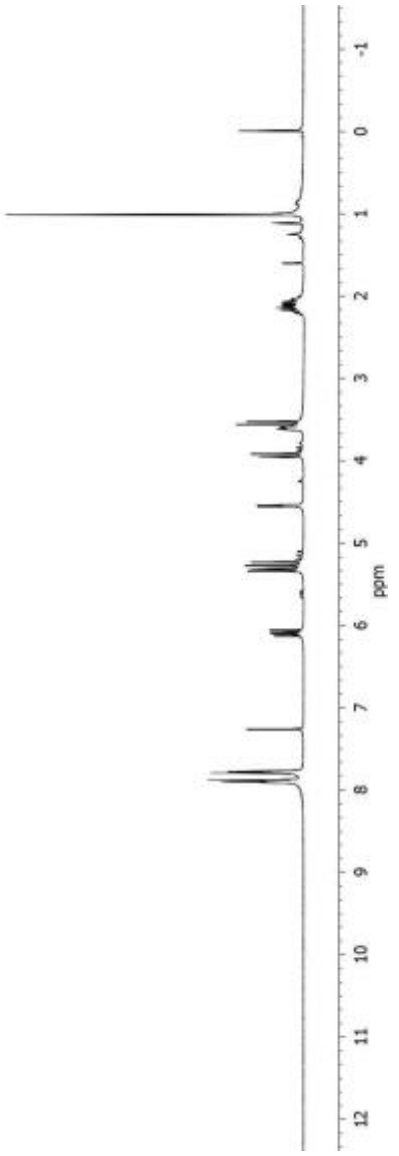
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.10 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.33 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.26 (dd, *J* = 17.7, 1.1 Hz, 1H), 4.54 (dd, *J* = 4.9, 1.3 Hz, 1H), 3.74 (dd, *J* = 156.5, 14.2 Hz, 2H), 3.65 – 3.59 (m, 1H), 2.26 – 1.99 (m, 2H), 1.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 137.8, 134.5, 131.6, 126.8 (q, *J* = 277.0 Hz), 123.8, 117.0, 68.6 (d, *J* = 2.7 Hz), 46.7, 44.1, 36.2 (q, *J* = 27.5 Hz), 18.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.9 (t, *J* = 10.8 Hz).

HRMS (CI) Calcd. For $C_{16}H_{17}NO_3F_3$ $[M+H]^+$: 328.1161, Found: 328.1163.

FTIR (neat): 3470, 2978, 1772, 1702, 1613, 1469, 1434, 1394, 1380, 1350, 1272, 1253, 1213, 1110, 1084, 1010, 947, 922, 903, 877, 842, 796, 759, 722 cm^{-1}.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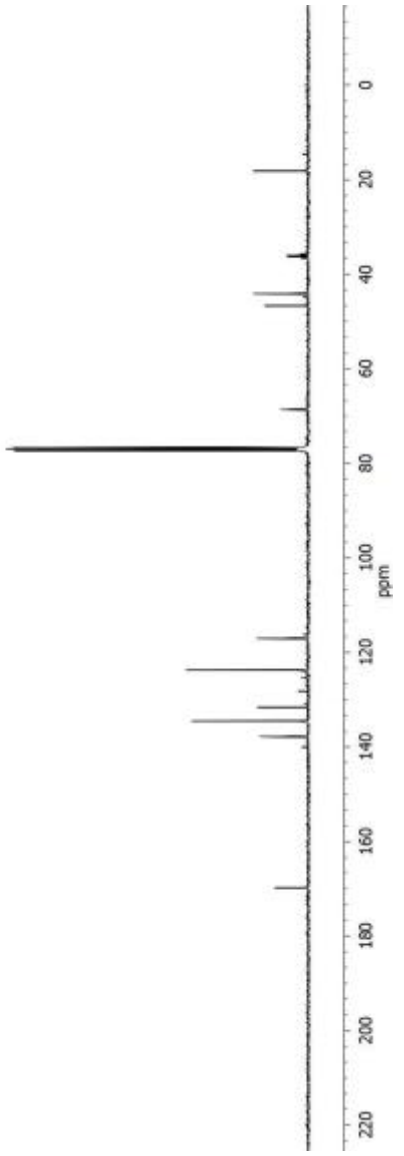
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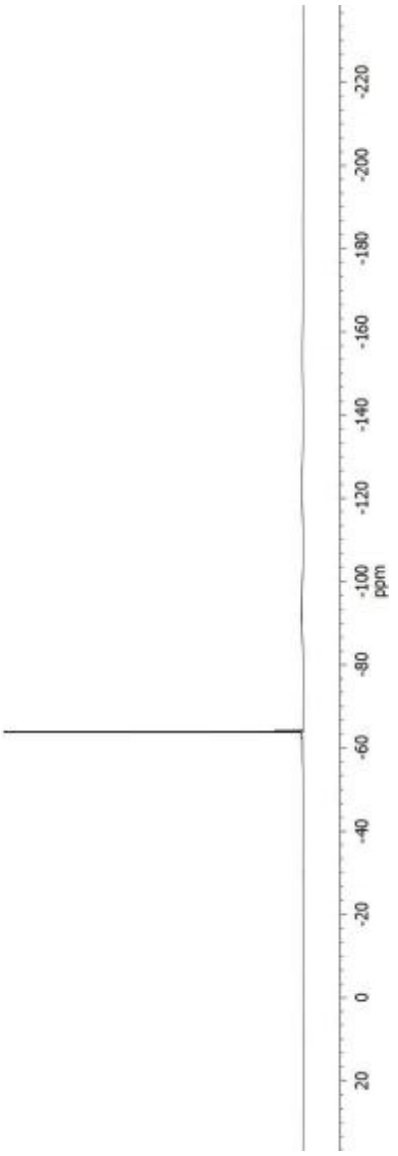
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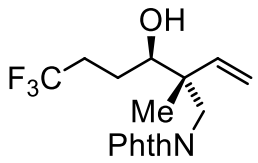
2-(6,6,6-trifluoro-3-hydroxy-2-methyl-2-vinylhexyl)isoindoline-1,3-dione (6.3o)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2b** and THF (0.2 mL, 1.0 M with respect to alcohol) at 95 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (58.0 mg, 85%, 5:1 *dr*) as a yellow oil.

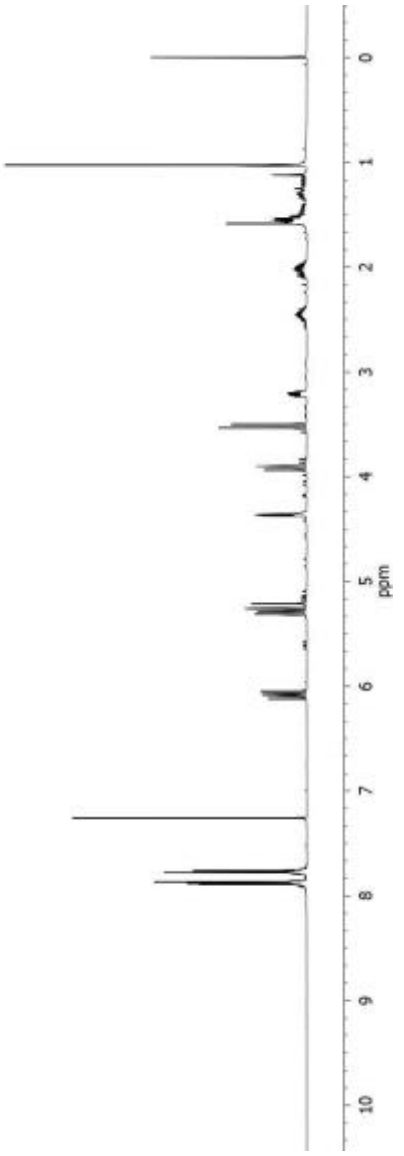
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.08 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.30 (dd, *J* = 11.0, 0.8 Hz, 1H), 5.24 (dd, *J* = 17.7, 1.2 Hz, 1H), 4.36 (dd, *J* = 4.8, 1.6 Hz, 1H), 3.72 (dd, *J* = 160.5, 14.1 Hz, 2H), 3.25 – 3.16 (m, 1H), 2.52 – 2.35 (m, 1H), 2.13 – 1.94 (m, 1H), 1.58 – 1.50 (m, 2H), 1.03 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 138.6, 134.5, 131.6, 127.5 (q, *J* = 272.1 Hz), 123.7, 116.4, 72.6, 46.8, 44.8, 31.3 (q, *J* = 28.6 Hz), 23.8 (d, *J* = 2.7 Hz), 18.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.3 (t, *J* = 11.1 Hz).

HRMS (CI) Calcd. For $C_{17}H_{19}NO_3F_3$ $[M+H]^+$: 342.1317, Found: 342.1319.

FTIR (neat): 3470, 2918, 1910, 1772, 1702, 1613, 1469, 1452, 1436, 1393, 1333, 1289, 1252, 1228, 1190, 1128, 1084, 1018, 927, 850, 795, 756, 721, 684 cm^{-1}.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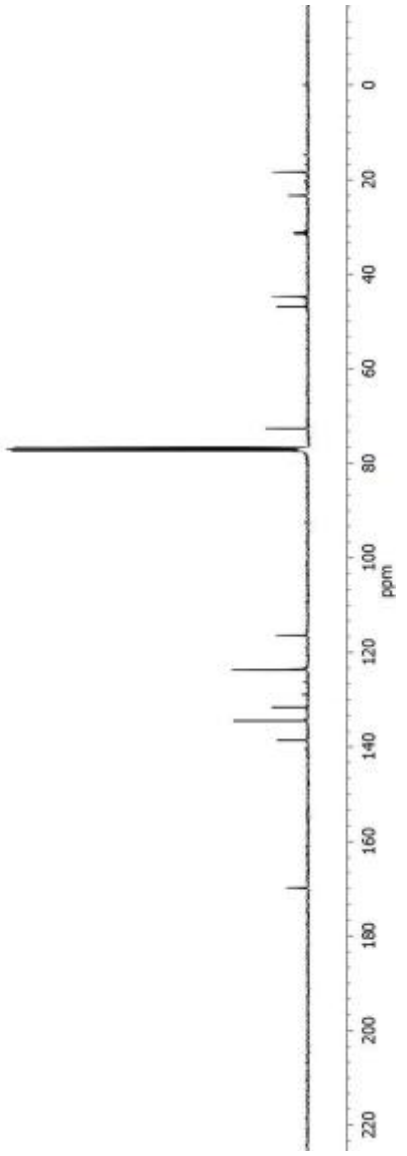
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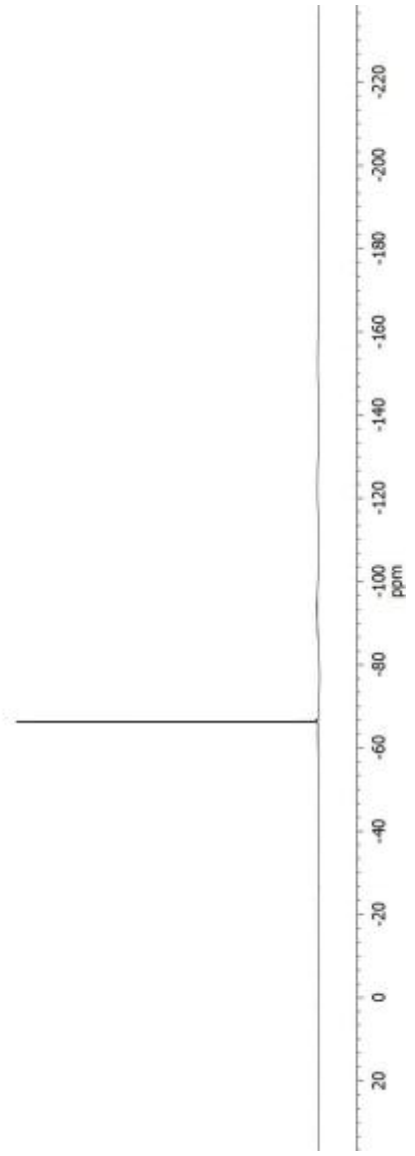
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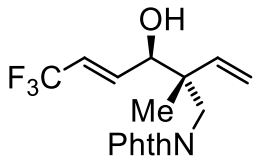
(*E*)-2-(6,6,6-trifluoro-3-hydroxy-2-methyl-2-vinylhex-4-en-1-yl)isoindoline-1,3-dione (6.3p)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2b** and THF (2.0 mL, 0.1 M with respect to alcohol) at 95 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 15% EtOAc/hexane) to furnish the title compound (59.0 mg, 87%, 6:1 *dr*) as a yellow oil.

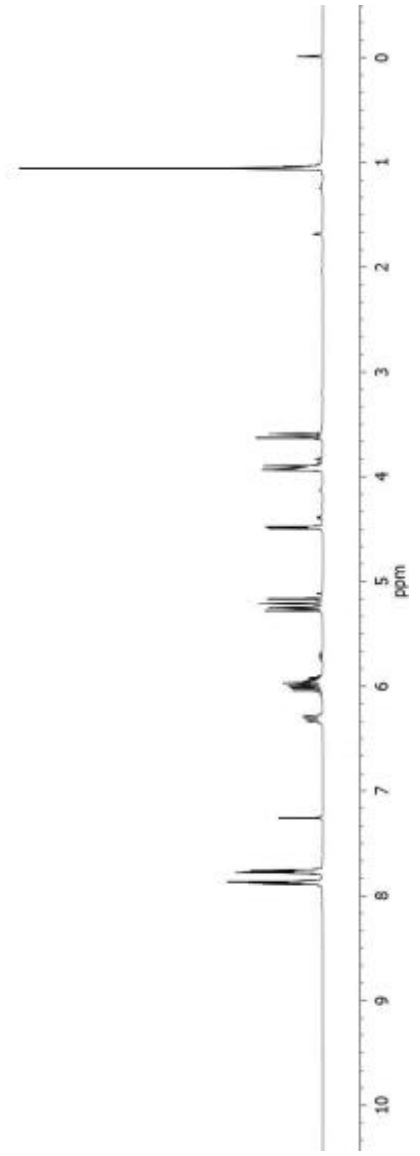
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.4, 3.1 Hz, 2H), 6.36 – 6.26 (m, 1H), 6.01 (dd, *J* = 17.7, 11.0 Hz, 1H), 5.98 – 5.88 (m, 1H), 5.26 (d, *J* = 11.0 Hz, 1H), 5.19 (d, *J* = 17.7 Hz, 1H), 4.49 (d, *J* = 5.0 Hz, 1H), 3.95 – 3.91 (m, 1H), 3.76 (dd, *J* = 122.3, 14.2 Hz, 2H), 1.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 138.1, 137.6 (q, *J* = 6.3 Hz), 134.5, 131.6, 123.7, 123.1 (q, *J* = 269.3 Hz), 120.1 (q, *J* = 33.7 Hz), 116.6, 72.7, 46.6, 44.3, 18.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.0 – -64.1 (m).

HRMS (CI) Calcd. For $C_{17}H_{17}NO_3F_3$ $[M+H]^+$: 340.1161, Found: 340.1159.

FTIR (neat): 3465, 2981, 1772, 1701, 1613, 1469, 1435, 1417, 1393, 1325, 1268, 1190, 1115, 1093, 1018, 963, 946, 920, 895, 868, 795, 721 cm^{-1}.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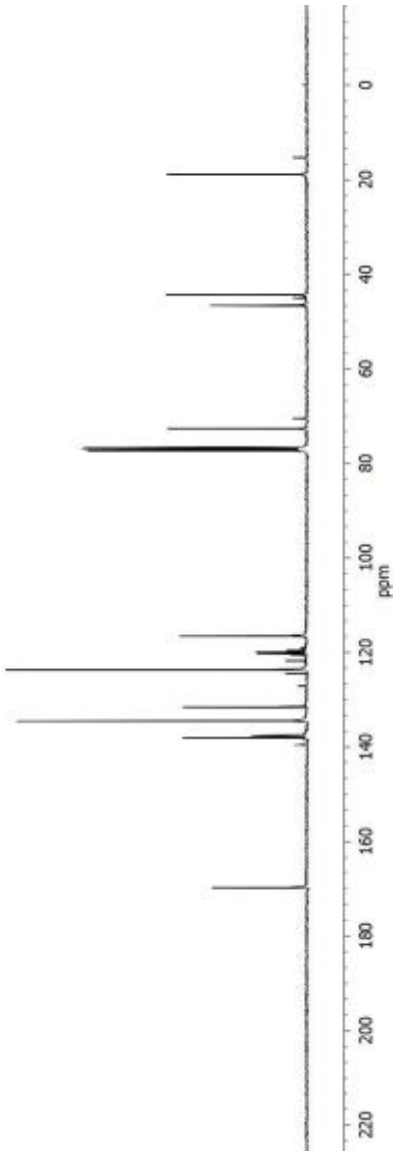
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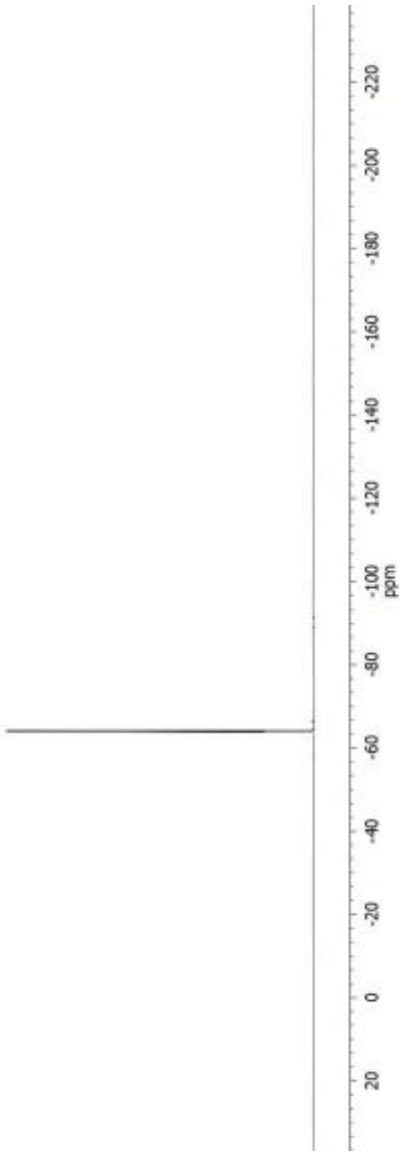
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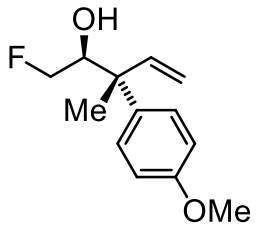
1-fluoro-3-(4-methoxyphenyl)-3-methylpent-4-en-2-ol (6.3e)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2c** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 72 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 10% EtOAc/hexane) to furnish the title compound (26.9 mg, 60%, >20:1 *dr*) as a yellow oil.

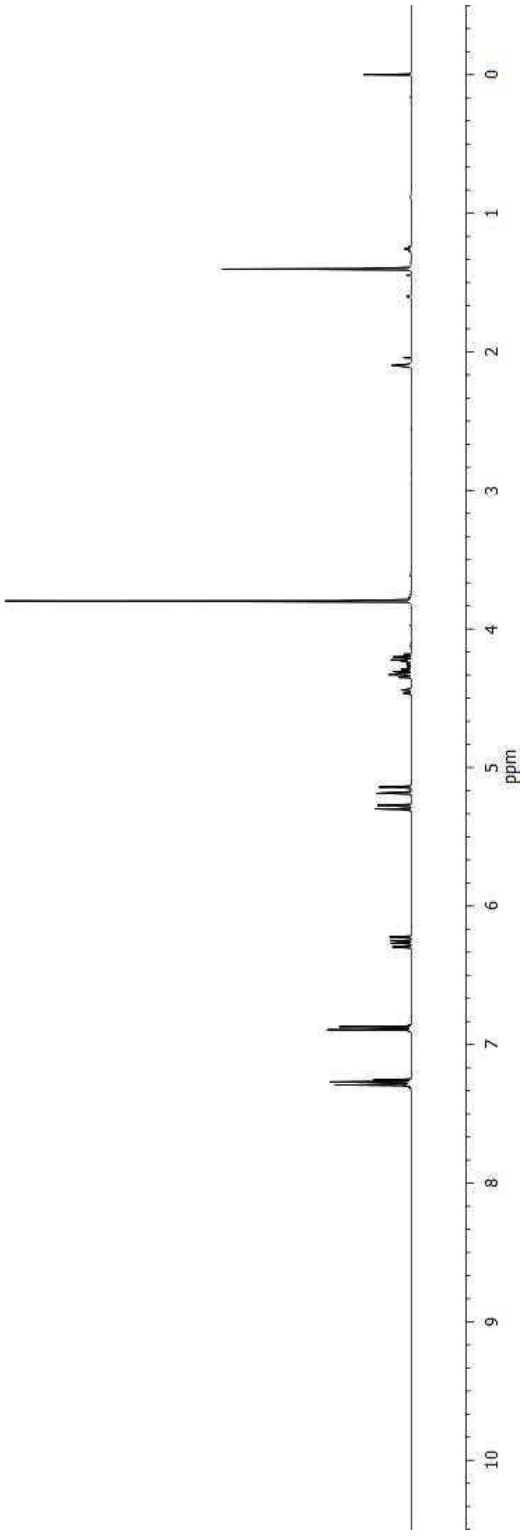
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.26 (m, 2H), 6.91 – 6.85 (m, 2H), 6.26 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.29 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.16 (dd, *J* = 17.7, 1.1 Hz, 1H), 4.48 – 4.17 (m, 3H), 3.80 (s, 3H), 2.10 (s, 1H), 1.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 142.3, 135.0, 127.8, 114.7, 113.9, 85.1 (d, *J* = 166.3 Hz), 75.7 (d, *J* = 17.6 Hz), 55.2, 46.9 (d, *J* = 6.9 Hz), 20.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -228.5 – -229.1 (m).

HRMS (ESI) Calcd. For $C_{13}H_{17}FO_2$ $[M+Na]^+$: 247.1150, Found: 247.1110.

FTIR (neat): 3478, 2966, 2835, 2360, 1635, 1609, 1579, 1511, 1463, 1414, 1374, 1294, 1248, 1183, 1095, 1057, 1031, 1008, 910, 829, 794, 731 cm^{-1}.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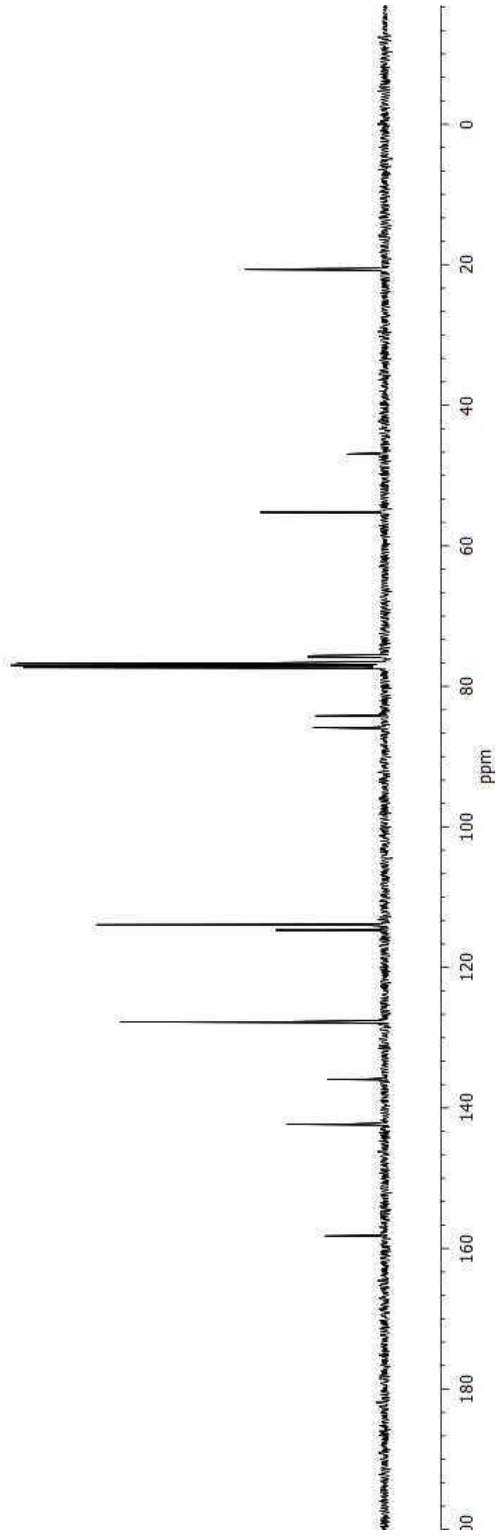
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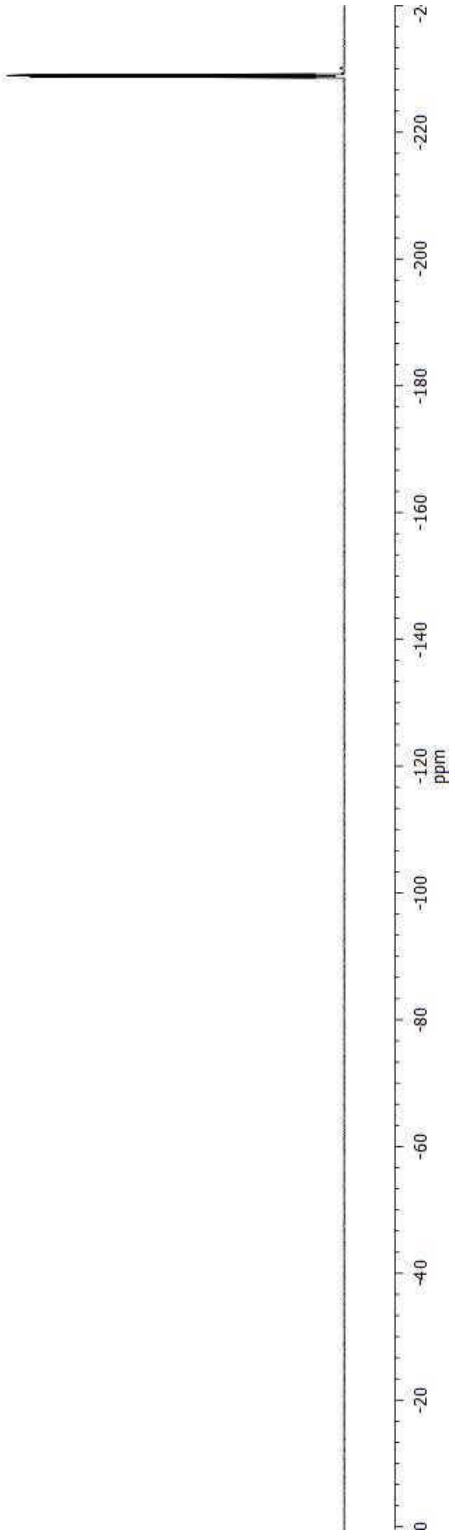
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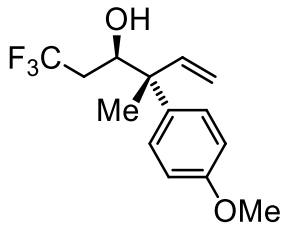
1,1,1-trifluoro-4-(4-methoxyphenyl)-4-methylhex-5-en-3-ol (6.3f)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2c** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (47.7 mg, 86%, >20:1 *dr*) as a yellow oil.

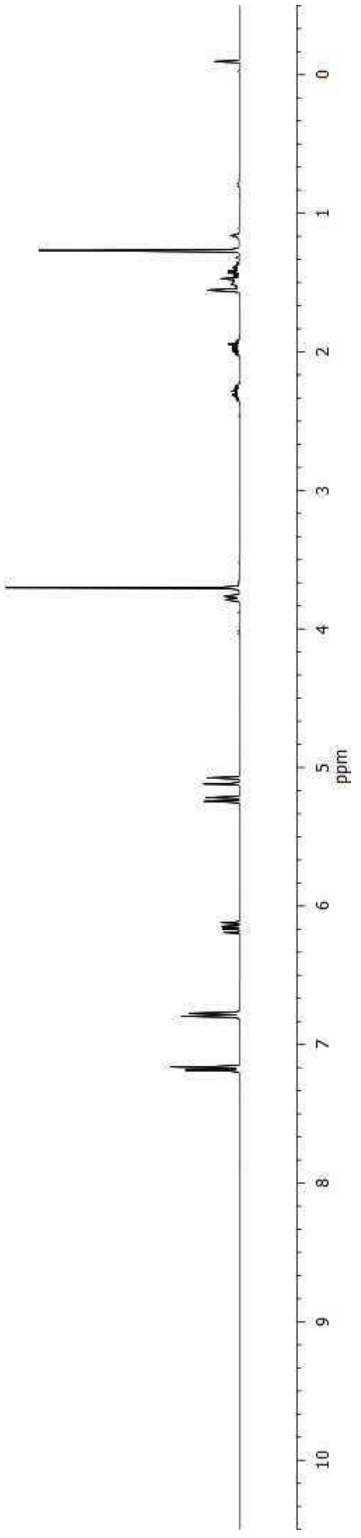
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, J = 9.3 Hz, 2H), 6.78 (d, J = 8.4 Hz, 2H), 6.25 (dd, J = 17.7, 10.9 Hz, 1H), 5.33 (dd, J = 10.9, 1.1 Hz, 1H), 5.19 (dd, J = 17.7, 1.1 Hz, 1H), 4.35 – 4.27 (m, 1H), 3.80 (s, 3H), 2.17 – 2.02 (m, 2H), 1.90 – 1.86 (m, 1H), 1.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 142.0, 136.0, 126.9 (q, J = 277.2 Hz), 115.5, 114.1, 71.5 (d, J = 2.4 Hz), 55.2, 48.7, 36.4 (q, J = 27.4 Hz), 19.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.6 (t, J = 10.2 Hz).

HRMS (ESI) Calcd. For $C_{14}H_{17}F_3O_2$ $[M+Na]^+$: 297.1073, Found: 297.1071.

FTIR (neat): 3538, 2977, 1609, 1512, 1464, 1412, 1376, 1328, 1292, 1250, 1182, 1122, 1032, 907, 876, 829, 794, 729 cm^{-1}.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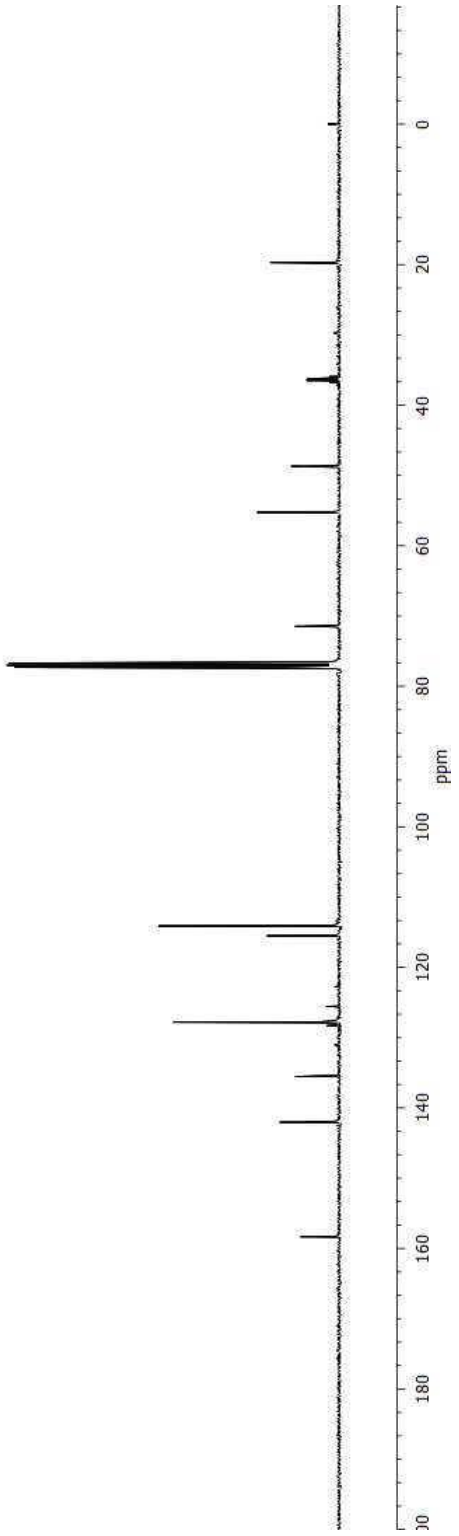
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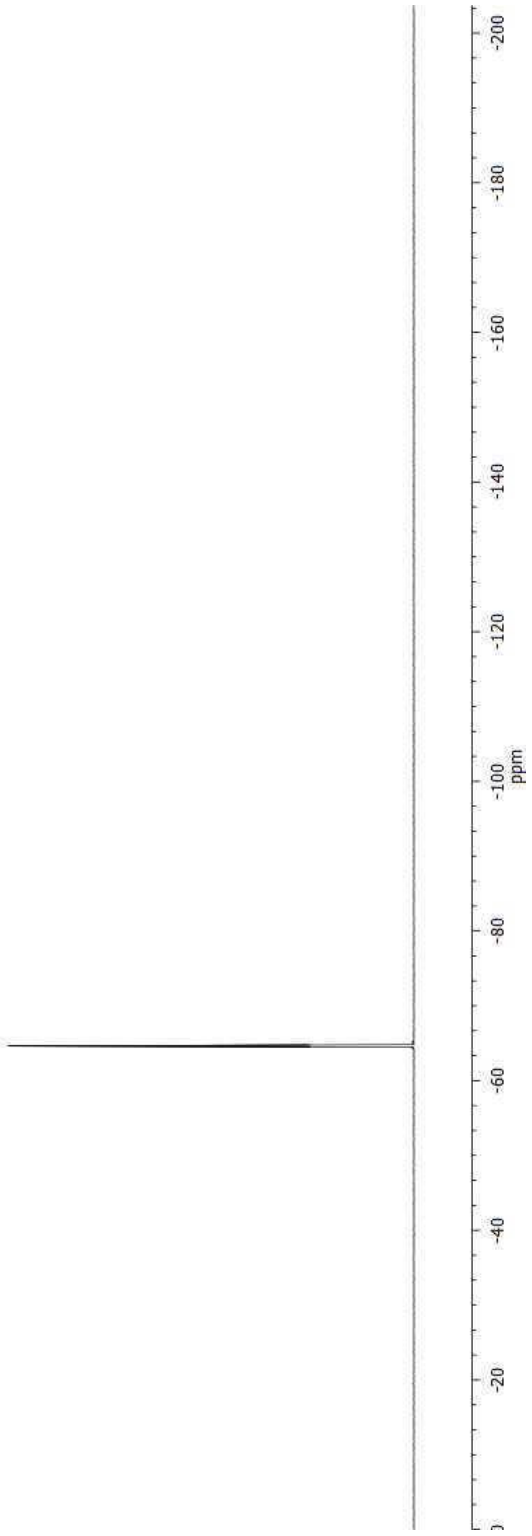
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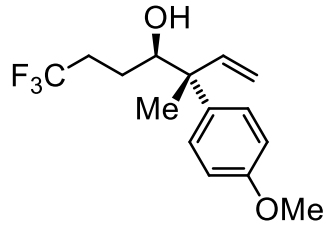
7,7,7-trifluoro-3-(4-methoxyphenyl)-3-methylhept-1-en-4-ol (6.3g)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2c** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (50.7 mg, 88%, >20:1 *dr*) as a yellow oil.

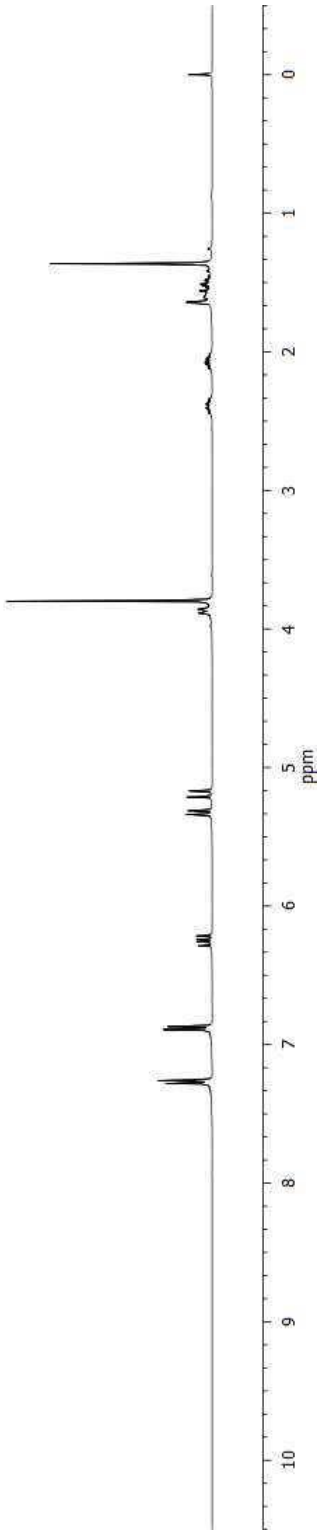
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.25 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.33 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.19 (dd, *J* = 17.7, 1.1 Hz, 1H), 3.90 – 3.84 (m, 1H), 3.80 (s, 3H), 2.53 – 2.31 (m, 1H), 2.18 – 1.92 (m, 1H), 1.69 – 1.41 (m, 3H), 1.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 142.3, 136.5, 127.7, 127.4 (q, *J* = 276.1 Hz), 115.2, 114.0, 76.2, 55.2, 48.9, 31.3 (q, *J* = 28.6 Hz), 23.8 (d, *J* = 2.7 Hz), 20.1 (s).

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.3 (t, *J* = 10.2 Hz).

HRMS (ESI) Calcd. For $C_{15}H_{19}F_3O_2$ $[M+Na]^+$: 311.1229, Found: 311.1229.

FTIR (neat): 3546, 2985, 1585, 1561, 1416, 1380, 1287, 1253, 1220, 1136, 1093, 1048, 1017, 907, 858, 799, 730, 693 cm^{-1}.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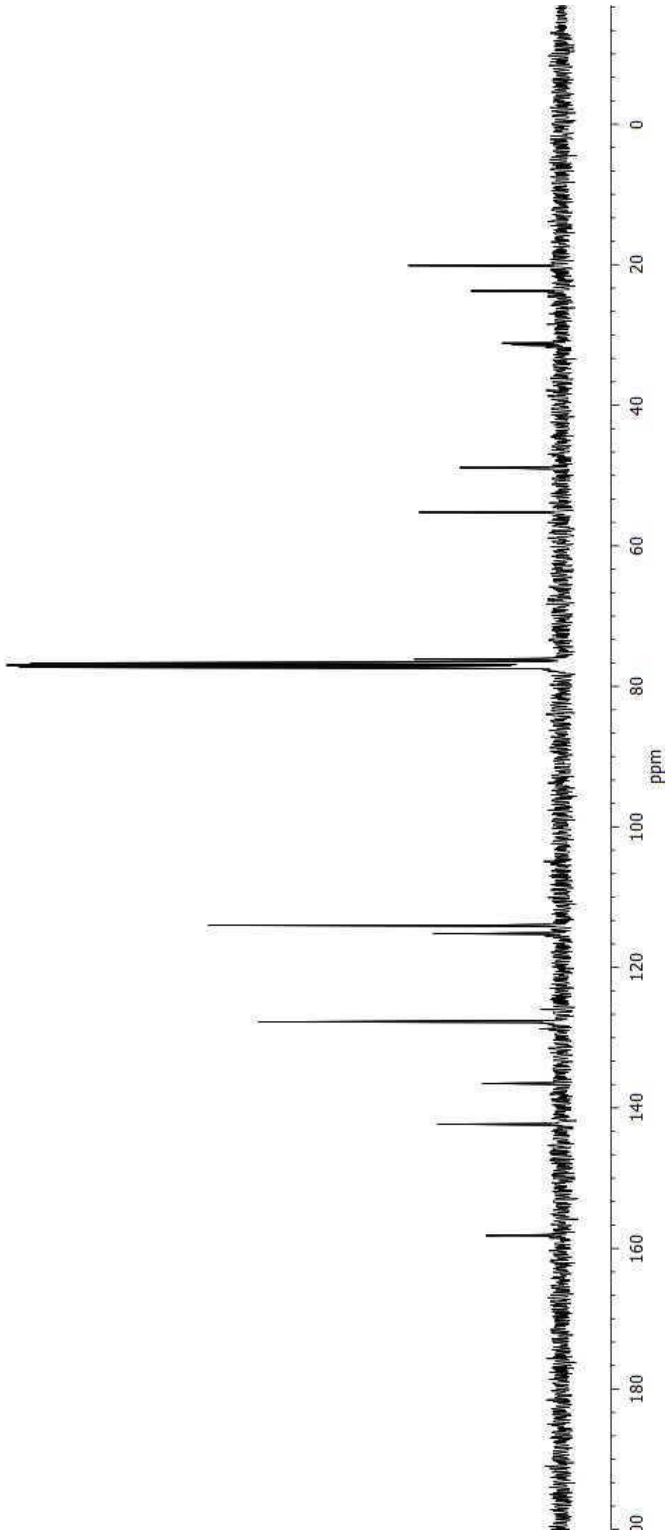
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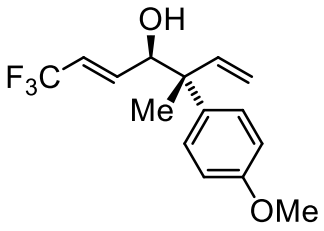
(*E*)-7,7,7-trifluoro-3-(4-methoxyphenyl)-3-methylhepta-1,5-dien-4-ol (6.3h)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2c** and THF (2.0 mL, 0.1 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (38.9 mg, 68%, >20:1 *dr*) as a yellow oil.

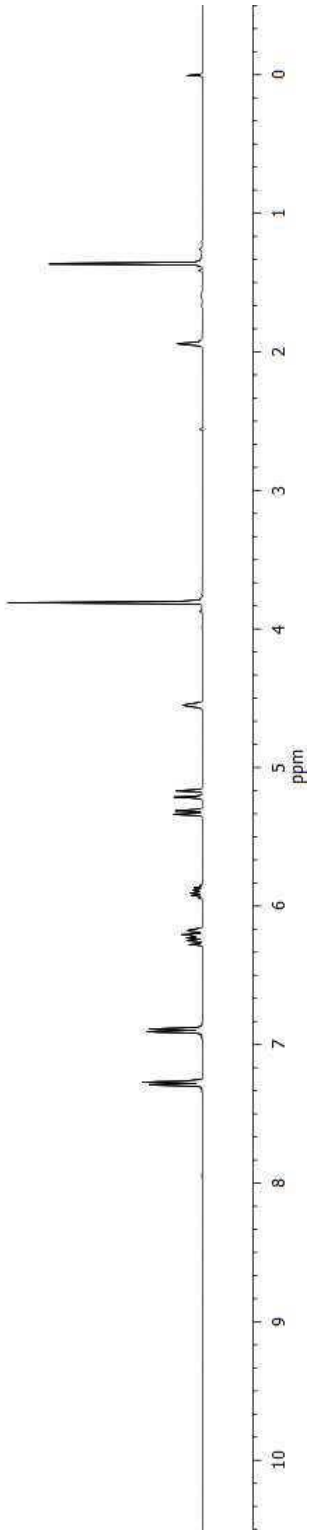
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 9.3 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.32 – 6.12 (m, 2H), 5.96 – 5.83 (m, 1H), 5.33 (d, J = 10.9 Hz, 1H), 5.19 (d, *J* = 17.6 Hz, 1H), 4.55 (s, 1H), 3.81 (s, 3H), 1.94 (s, 1H), 1.37 (s,3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 142.2, 138.2 (q, *J* = 6.2 Hz), 135.3, 127.9, 123.0 (q, *J* = 269.4 Hz), 119.8 (q, *J* = 33.9 Hz), 115.5, 75.7, 55.3, 48.8, 19.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.0 – -65.0 (m).

HRMS (ESI) Calcd. For $C_{15}H_{17}F_3O_2$ $[M+Na]^+$: 309.1073, Found: 309.1071.

FTIR (neat): 3565, 2837, 1609, 1511, 1465, 1290, 1251, 1184, 1114, 1092, 1069, 1031, 979, 908, 829, 790, 732, 674 cm^{-1}.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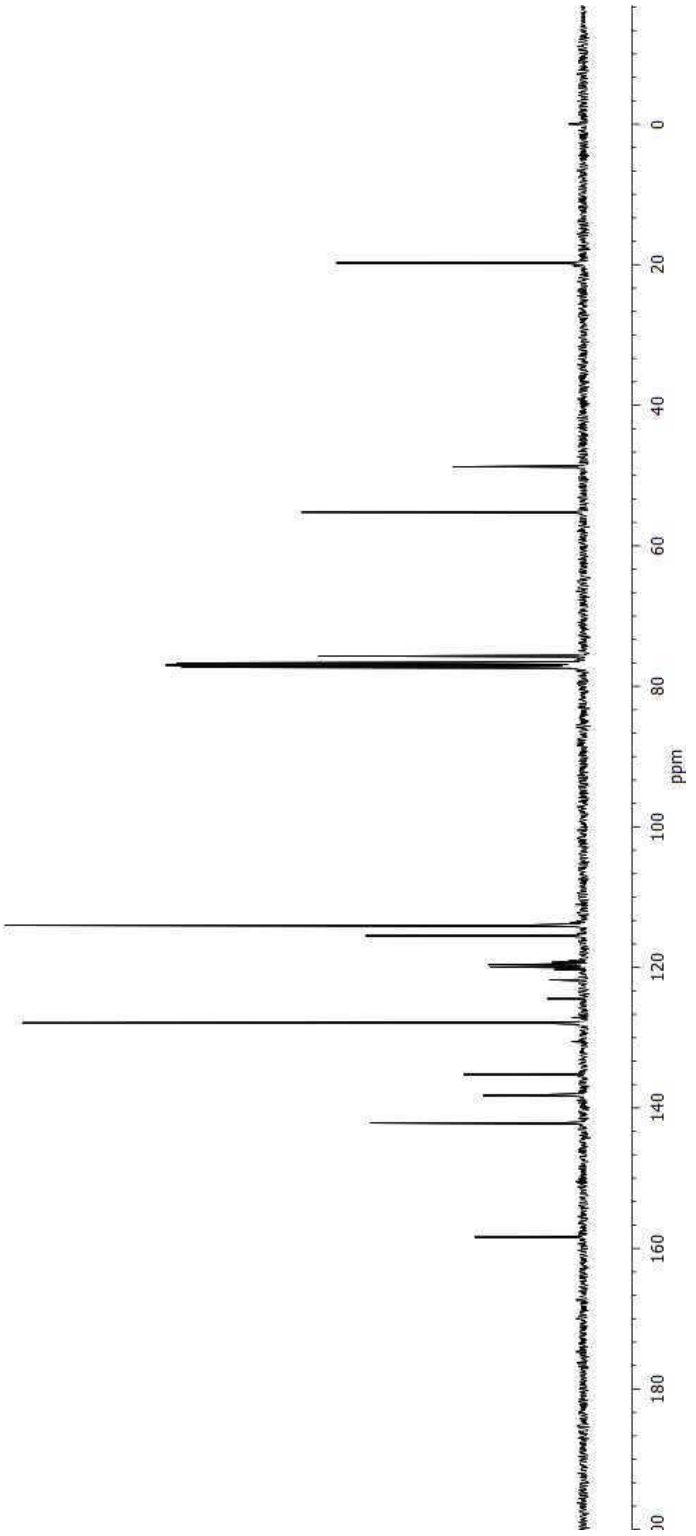
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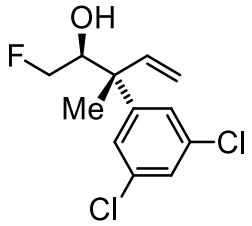
3-(3,5-dichlorophenyl)-1-fluoro-3-methylpent-4-en-2-ol (6.3i)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2d** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 72 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 5% EtOAc/hexane) to furnish the title compound (34.2 mg, 65%, >20:1 *dr*) as a yellow oil.

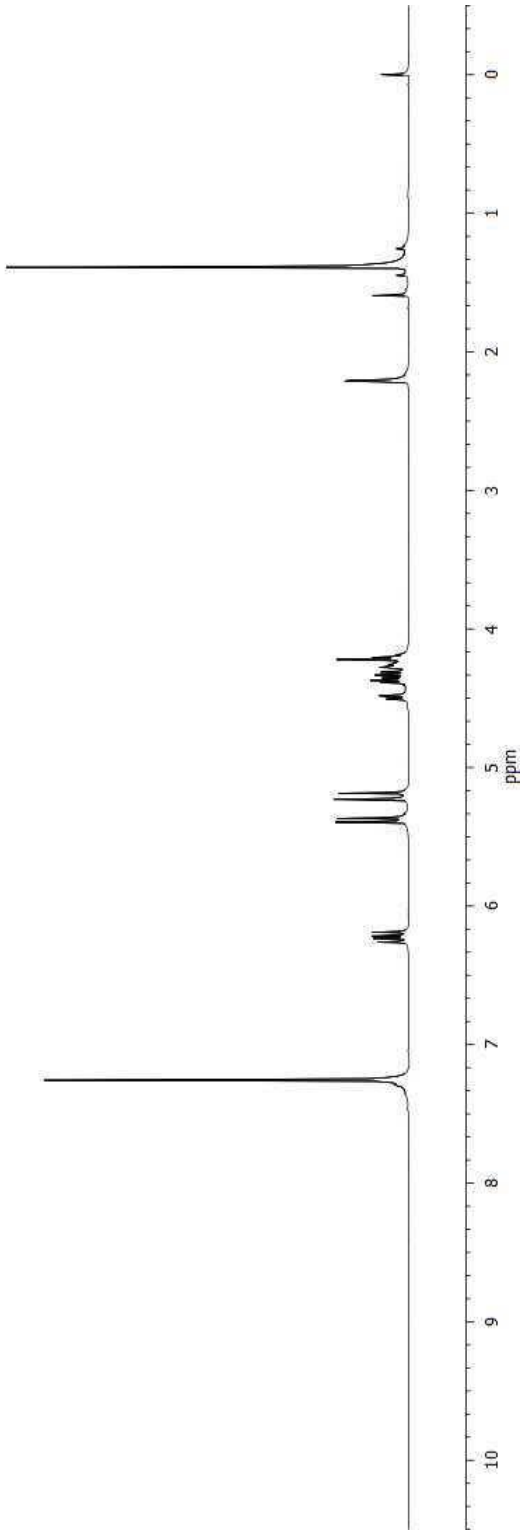
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (s, 3H), 6.22 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.38 (d, *J* = 10.9 Hz, 1H), 5.21 (d, *J* = 17.7 Hz, 1H), 4.54 – 4.11 (m, 3H), 2.21 (d, J = 2.1 Hz, 1H), 1.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.29, 140.4, 135.1, 127.0, 125.6, 116.3, 84.7 (d, *J* = 166.8 Hz), 75.2 (d, *J* = 18.2 Hz), 47.6 (d, *J* = 6.6 Hz), 21.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -229.0 (td, *J* = 49.6, 15.6 Hz).

HRMS (CI) Calcd. For $C_{12}H_{14}Cl_2FO$ $[M+H]^+$: 263.0406, Found: 263.0407.

FTIR (neat): 3600, 2981, 1585, 1416, 1414, 1374, 1294, 1248, 1183, 1070, 1066, 1057, 1031, 1008, 916, 833, 794, 731 cm^{-1}.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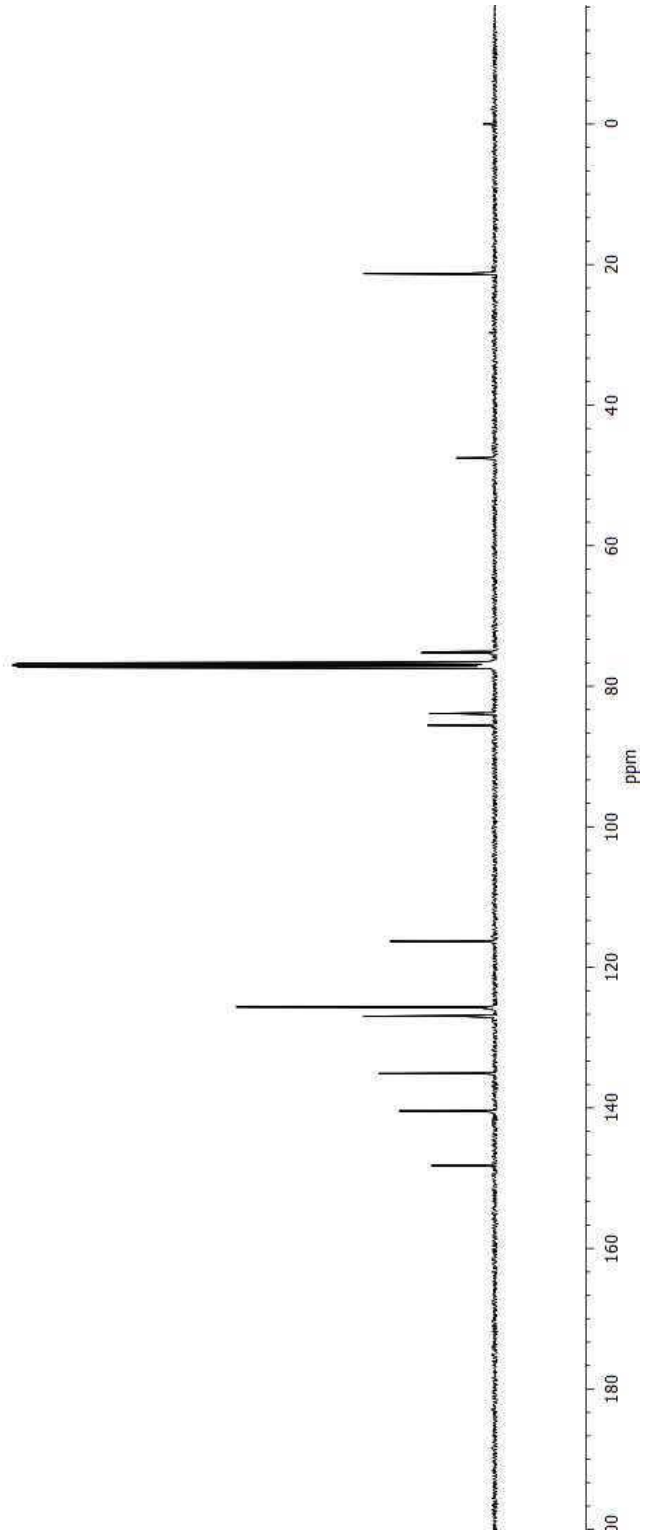
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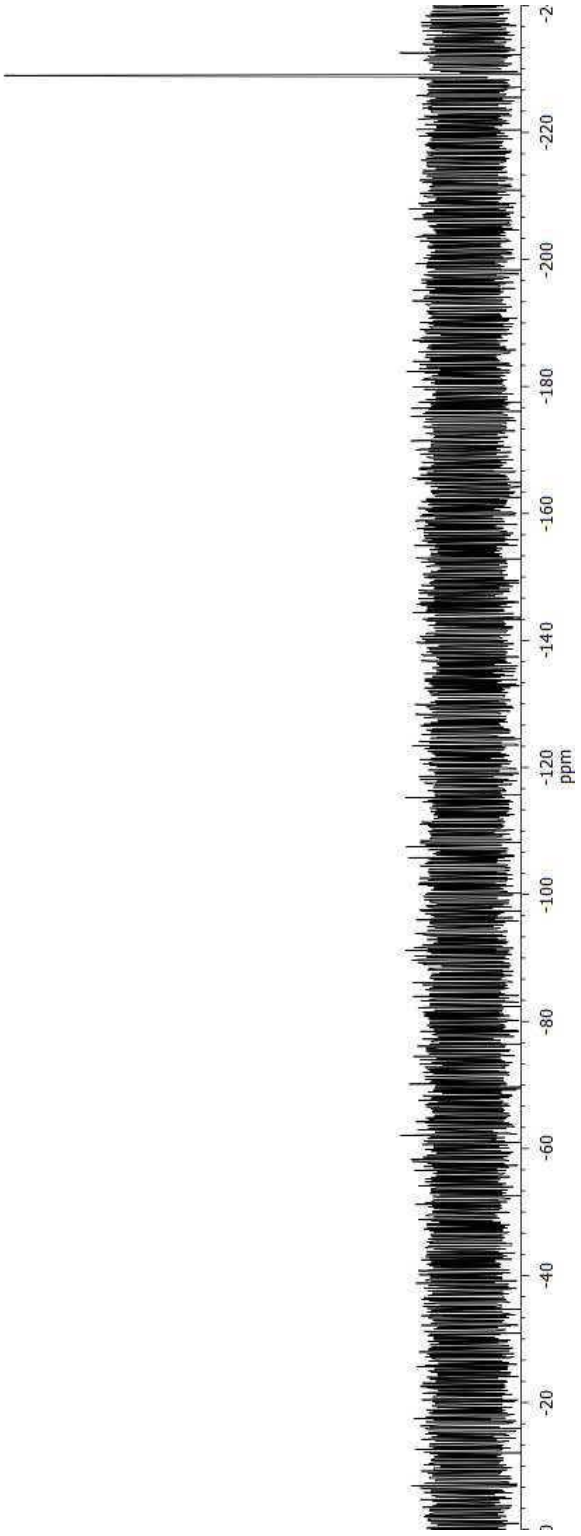
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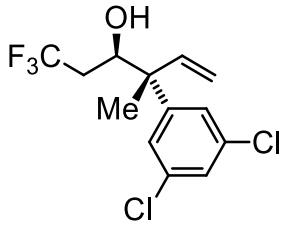
4-(3,5-dichlorophenyl)-1,1,1-trifluoro-4-methylhex-5-en-3-ol (6.3j)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2d** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (53.2 mg, 85%, >20:1 *dr*) as a yellow oil.

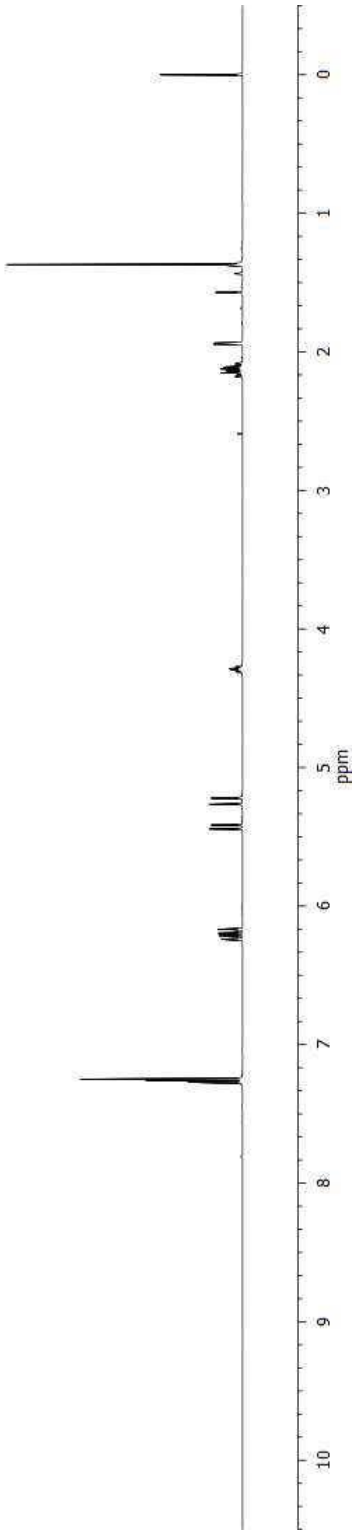
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.20 (m, 3H), 6.20 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.43 (dd, *J* = 10.9, 0.7 Hz, 1H), 5.24 (dd, *J* = 17.7, 0.7 Hz, 1H), 4.34 – 4.20 (m, 1H), 2.21 – 2.06 (m, 2H), 1.95 (d, *J* = 3.5 Hz, 1H), 1.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 140.4, 135.3, 127.2, 126.9 (q, *J* = 277.2 Hz), 125.7, 117.1, 71.3 (d, *J* = 2.5 Hz), 49.5, 36.7 (q, *J* = 27.3 Hz), 20.6

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.8 (t, *J* = 10.8 Hz).

HRMS (CI) Calcd. For $C_{13}H_{13}Cl_2F_3O$ $[M]^+$: 312.0296, Found: 312.0300.

FTIR (neat): 3515, 2923, 2360, 2342, 1585, 1561, 1415, 1382, 1325, 1255, 1120, 1008, 929, 907, 875, 857, 842, 799, 732, 691 cm^{-1}.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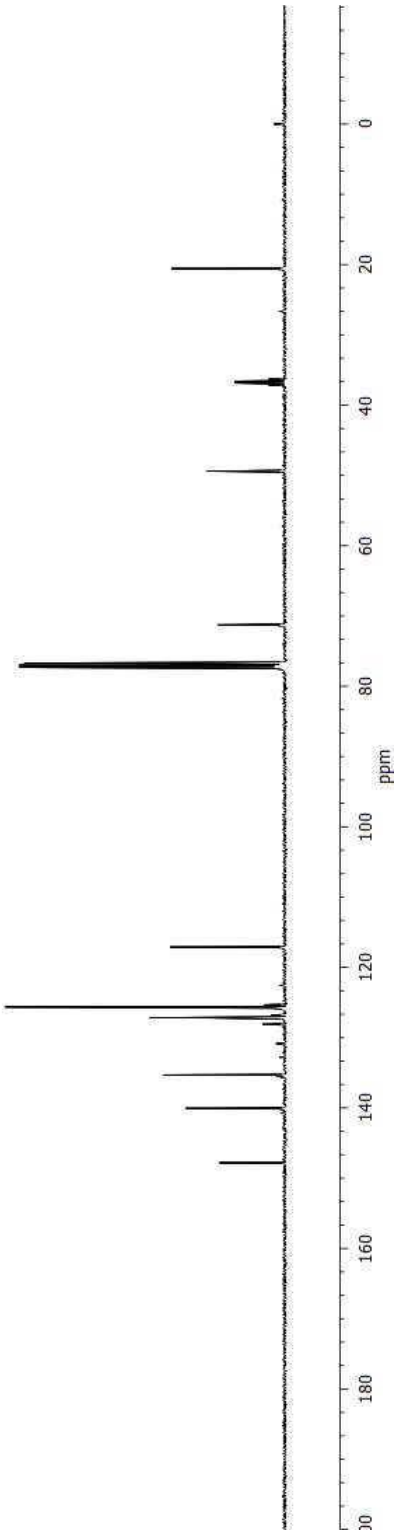
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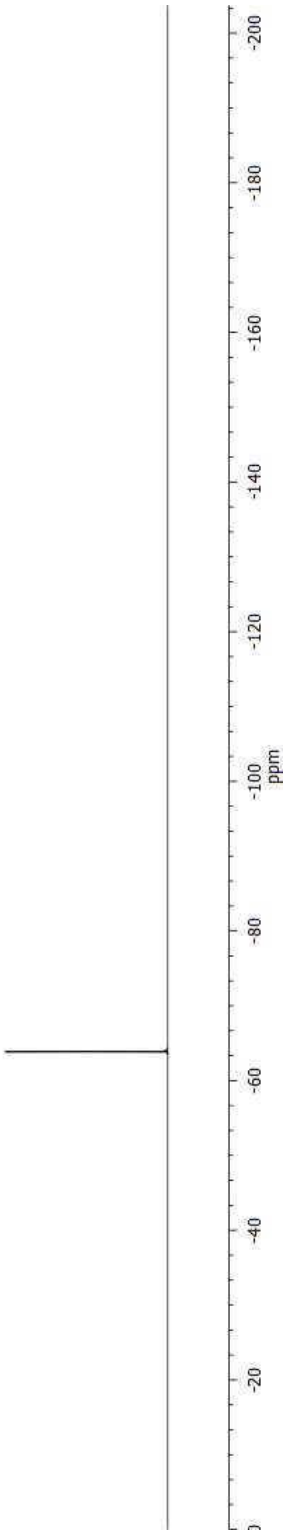
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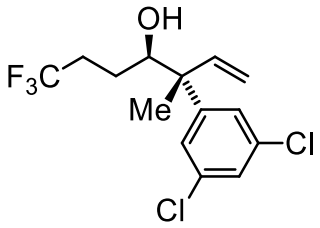
3-(3,5-dichlorophenyl)-7,7,7-trifluoro-3-methylhept-1-en-4-ol (6.3k)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2d** and THF (0.2 mL, 1.0 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (58.2 mg, 89%, >20:1 *dr*) as a yellow oil.

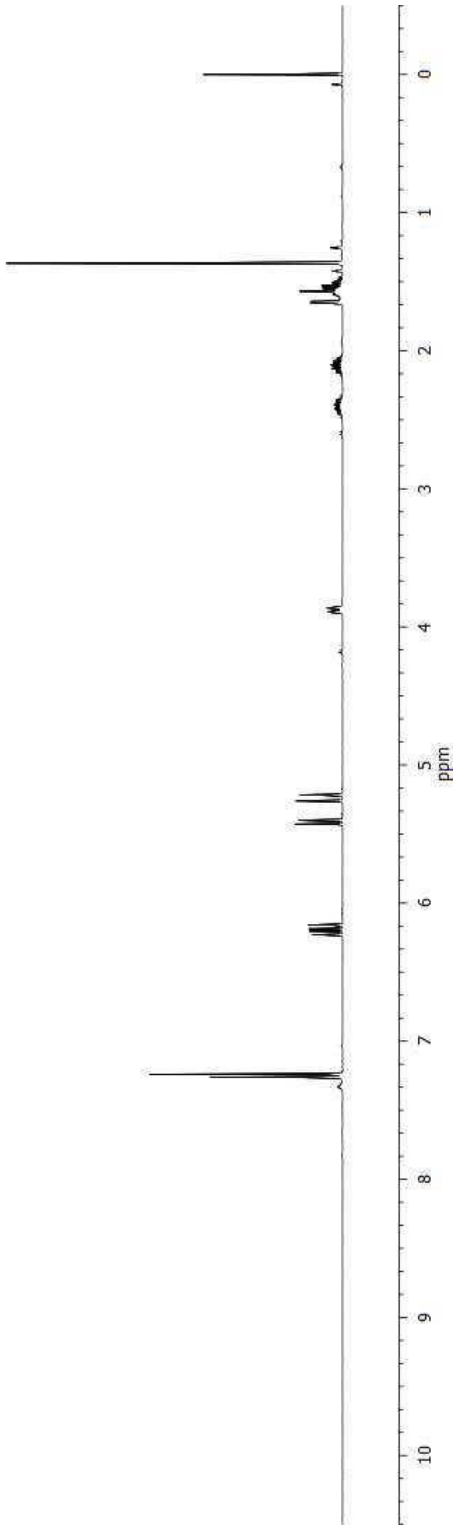
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.21 (m, 3H), 6.19 (dd, *J* = 17.7, 10.9 Hz, 1H), 5.40 (dd, *J* = 10.9, 0.7 Hz, 1H), 5.24 (dd, *J* = 17.6, 0.7 Hz, 1H), 3.88 (dt, *J* = 10.4, 3.2 Hz, 1H), 2.50 – 2.30 (m, 1H), 2.21 – 2.02 (m, 1H), 1.67 – 1.46 (m, 3H), 1.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7 140.7, 135.3, 127.3 (q, *J* = 276.1), 127.0, 125.6, 116.8, 75.9, 49.8, 31.1 (q, *J* = 28.6 Hz), 23.9, 20.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -65.9 (t, *J* = 11.0 Hz).

HRMS (CI) Calcd. For $C_{14}H_{15}Cl_2F_3O$ $[M]^+$: 326.0452, Found: 326.0426.

FTIR (neat): 3541, 2985, 1585, 1561, 1416, 1380, 1287, 1253, 1220, 1136, 1093, 1048, 1017, 907, 858, 799, 730, 693 cm^{-1}.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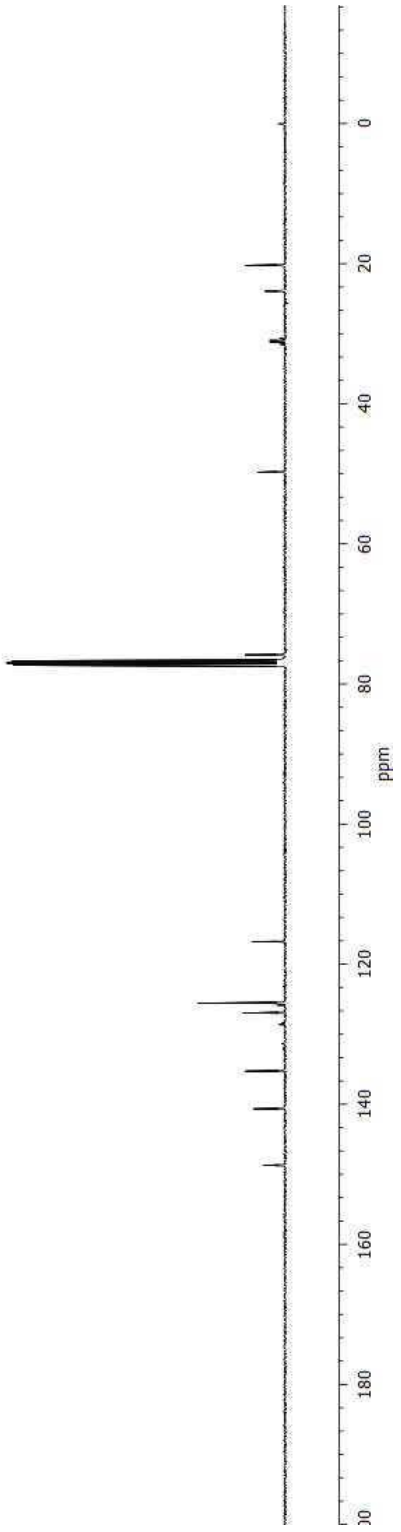
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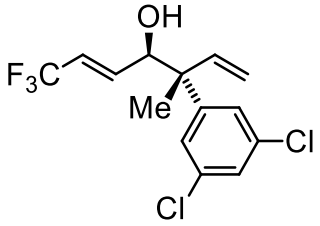
(*E*)-3-(3,5-dichlorophenyl)-7,7,7-trifluoro-3-methylhepta-1,5-dien-4-ol (6.3l)



The reaction was conducted in accordance with **General Procedure A** *via* allene **6.2d** and THF (4 mL, 0.05 M with respect to alcohol) at 75 °C for 48 hours. The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (52.0 mg, 80%, >20:1 *dr*) as a yellow oil.

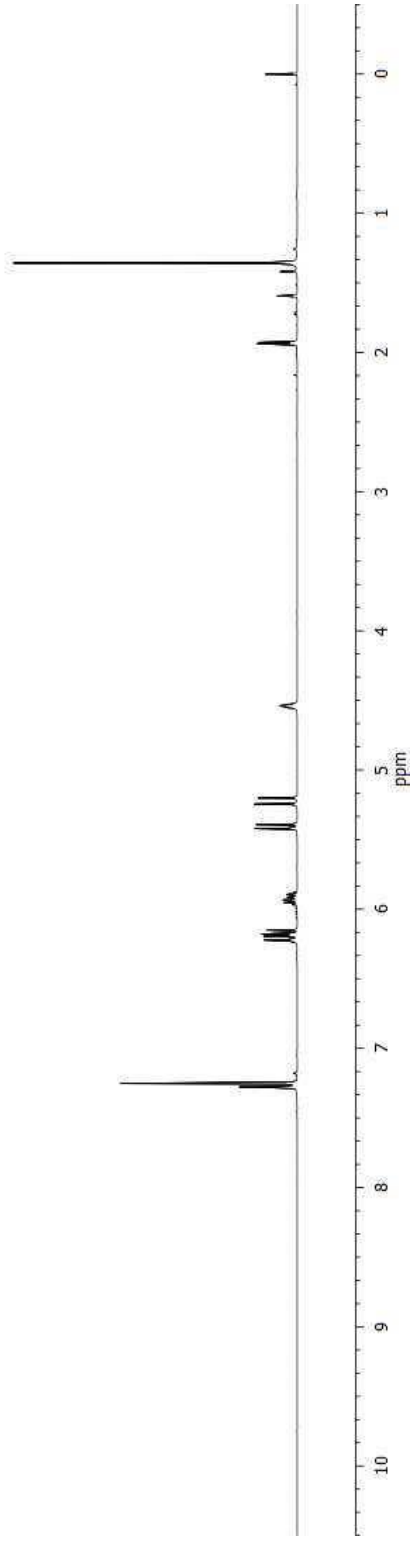
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.22 (m, 3H), 6.27 – 6.11 (m, 2H), 5.98 – 5.86 (m, 1H), 5.40 (dd, *J* = 10.8, 0.6 Hz, 1H), 5.23 (dd, *J* = 17.6, 0.6 Hz, 1H), 4.58 – 4.48 (m, 1H), 1.93 (d, *J* = 4.2 Hz, 1H), 1.36 (s,3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 141.9, 138.1 (q, *J* = 6.3 Hz), 128.7, 127.0, 126.8, 123.1 (q, *J* = 269.3 Hz), 120.8 (q, *J* = 34.0 Hz), 115.9, 75.6, 49.4, 19.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.1 – -64.2 (m).

HRMS (CI) Calcd. For $C_{14}H_{14}Cl_2F_3O$ $[M+H]^+$: 325.0374, Found: 325.0374.

FTIR (neat): 3469, 2982, 1682, 1585, 1561, 1416, 1383, 1312, 1265, 1123, 975, 931, 906, 858, 799, 730, 691 cm^{-1}.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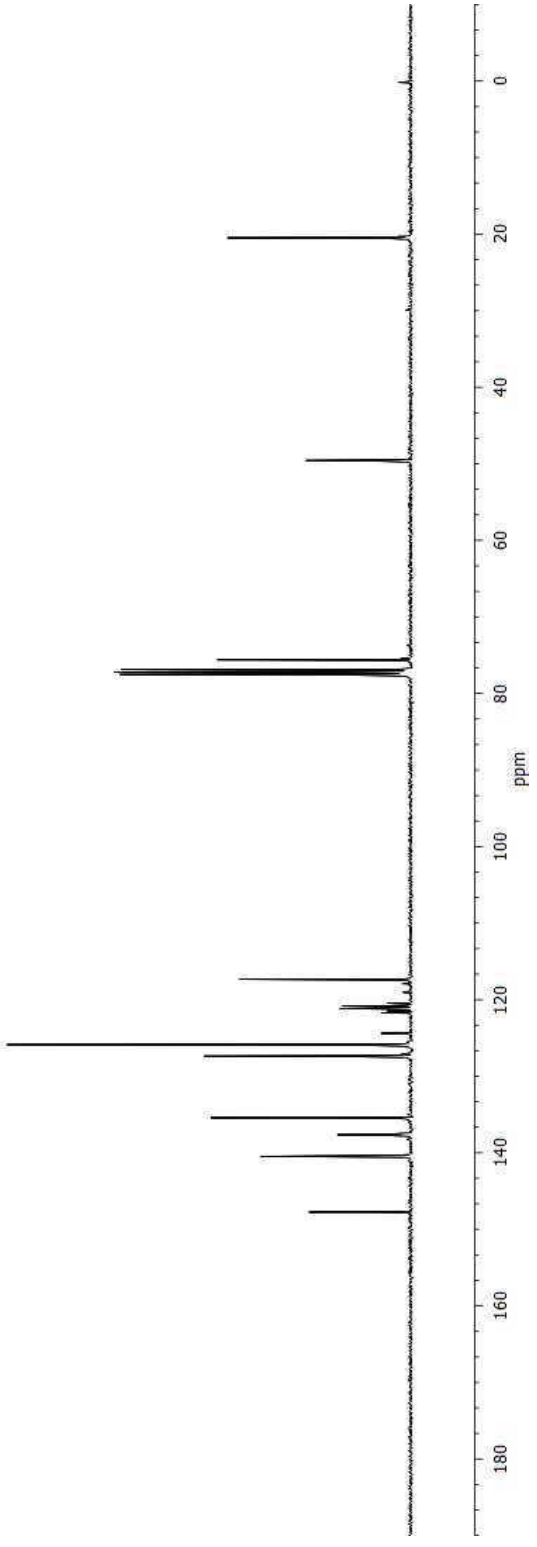
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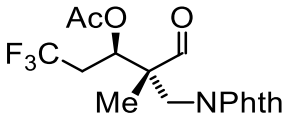
5-(1,3-dioxoisoindolin-2-yl)-1,1,1-trifluoro-4-formyl-4-methylpentan-3-yl acetate (6.3q)



In modification to literature procedure,[114] to a flame-dried 50 mL round-bottom flask charged with alcohol **6.3n** (130 mg, 0.400 mmol, 100 mol%) and CH_2Cl_2 (0.8 mL, 0.5 M) was added triethylamine (80 mg, 0.800 mmol, 200 mol%), *N,N*-dimethylaminopyridine (4.9 mg, 0.040 mmol, 10 mol%) and acetic anhydride (60 mg, 0.600 mmol, 150 mol%) at ambient temperature. After stirring for 2 hours, the reaction was quenched with pH 7 phosphate buffer (15 mL). The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2; 10% EtOAc/hexane) to provide the corresponding acetate (140 mg, 0.380 mmol, 95%) as a colorless oil, which was immediately subjected to ozonolysis.

In modification to literature procedure,[115] the acetate was dissolved in CH_2Cl_2 (15 mL, 0.03 M) and cooled to -78 °C. O_3 was directed into the solution until it turned deep blue. The resulting solution was purged with argon to remove the excess of O_3. Triphenylphosphine (189 mg, 1.90 mmol, 500 mol%) was added and the solution was allowed to warm up to room temperature with stirring over 4 hours. After evaporation of solvents, the residue was subjected to flash column chromatography (SiO_2; 20% EtOAc/hexane) to afford the title compound (109 mg, 78%) as a colorless oil.

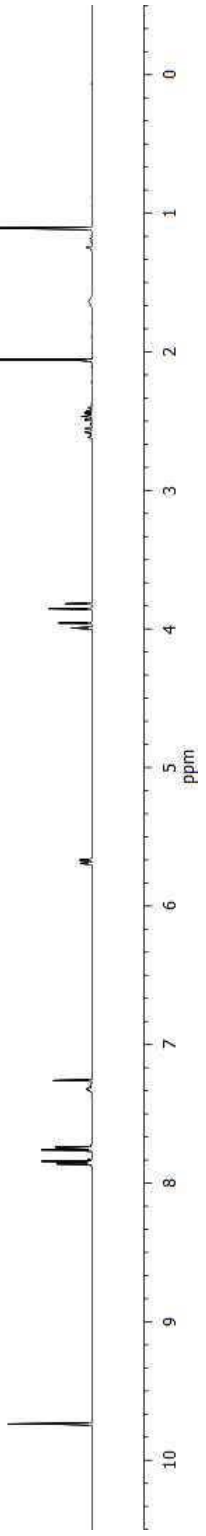
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 7.89 – 7.80 (m, 2H), 7.76 – 7.72 (m, 2H), 5.68 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.91 (dd, *J* = 55.3, 14.4 Hz, 2H), 2.63 – 2.37 (m, 2H), 2.06 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 169.4, 168.2, 134.5, 131.5, 125.6 (q, *J* = 271.1 Hz), 123.7, 67.7 (d, *J* = 2.7 Hz), 54.7, 39.7, 34.4 (q, *J* = 29.0 Hz), 20.6, 13.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ -63.9 (t, *J* = 10.2 Hz).

HRMS (ESI) Calcd. For $C_{17}H_{16}F_3NO_5$ $[M+Na]^+$: 394.0873, Found: 394.0877.

FTIR (neat): 3472, 2977, 1772, 1702, 1468, 1434, 1393, 1379, 1349, 1333, 1272, 1252, 1212, 1128, 1110, 946, 904, 904, 877, 841, 795, 721, 685 cm^{-1}.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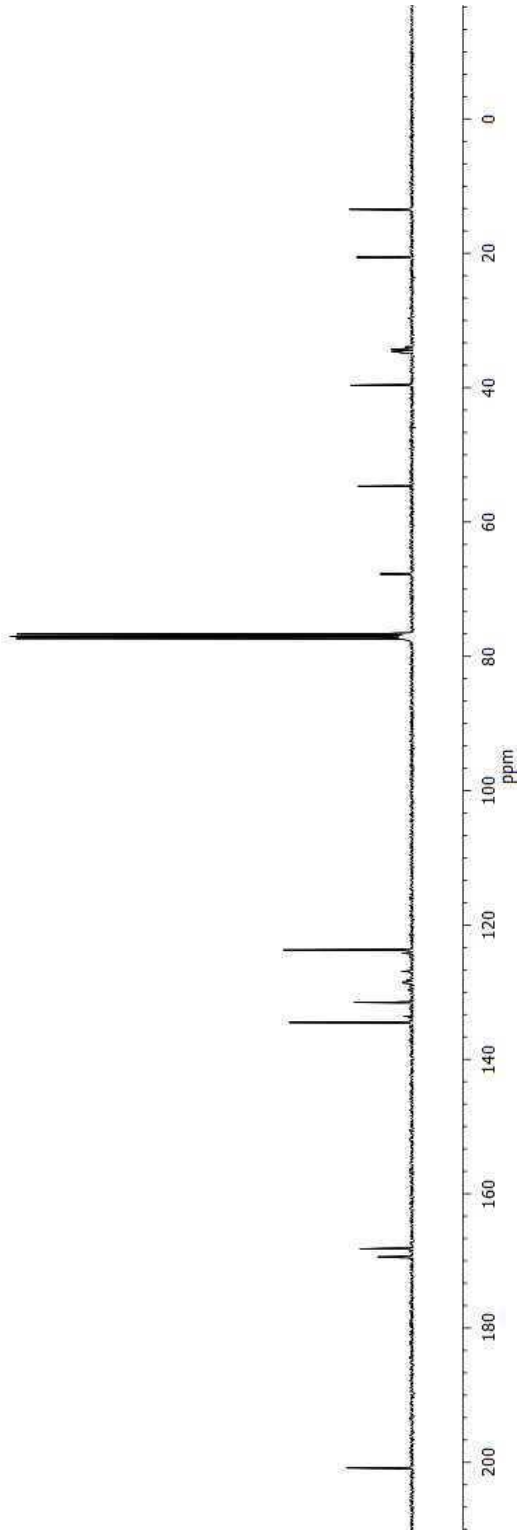
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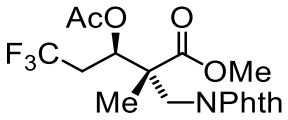
Methyl 3-acetoxy-2-((1,3-dioxoisoindolin-2-yl)methyl)-5,5,5-trifluoro-2 methylpentanoate (6.3r)



In modification to literature procedure,[115] a flamed-dried 50 mL round-bottom flask was charged with aldehyde **6.3q** (109 mg, 0.300 mmol, 100 mol%), THF (3 mL), and *t*-BuOH (3 mL). To this stirring solution was added 2.0 M 2-methyl-2-butene in THF (4.5 mL, 9.00 mmol, 3000 mol%), then an aqueous solution comprised of $NaClO_2$ (136 mg, 1.50 mmol, 500 mol%) and NaH_2PO_4 (207 mg, 0.057 mmol, 500 mol%) in H_2O (0.5 mL). The reaction was stirred at room temperature at ambient temperature for 4 hours, and then diluted with ethyl acetate (5 mL) and poured into brine (10 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was carried onto the next step without further purification.

To a solution of crude residue in CH_2Cl_2 (1.5 mL) and MeOH (1 mL) was added 2.0 M Me_3SiCHN_2 in hexanes (0.23 mL, 0.450 mmol, 150 mol%) at ambient temperature. After stirring for 10 minutes, the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 30% EtOAc/hexane) to afford the title compound (88.6 mg, 85% over two steps) as a white oil.

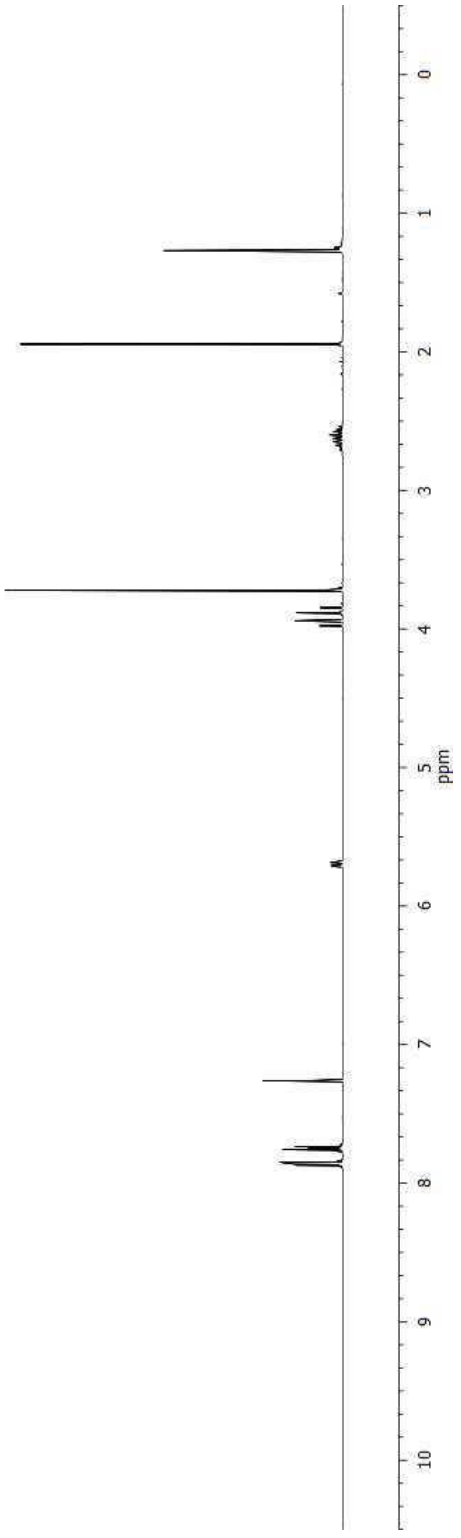
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 2H), 7.76 – 7.73 (m, 2H), 5.70 (dd, J = 10.0, 1.4 Hz, 1H), 3.91 (dd, J = 37.3, 14.4 Hz, 2H), 3.72 (s, 3H), 2.75 – 2.49 (m, 2H), 1.94 (s, 3H), 1.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 168.78, 168.1, 134.3, 131.7, 125.6 (q, J = 269.8 Hz), 123.6, 68.2 (d, J = 2.6 Hz), 52.7, 50.9, 41.1, 34.7 (q, J = 29.0 Hz), 20.6, 16.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.3 (t, J = 10.2 Hz).

HRMS (ESI) Calcd. For $C_{18}H_{18}F_3NO_6$ $[M+Na]^+$: 424.0978, Found: 424.0980.

FTIR (neat): 3467, 2954, 2253, 1772, 1704, 1469, 1436, 1394, 1379, 1349, 1273, 1253, 1131, 1084, 1010, 905, 841, 722 cm^{-1}.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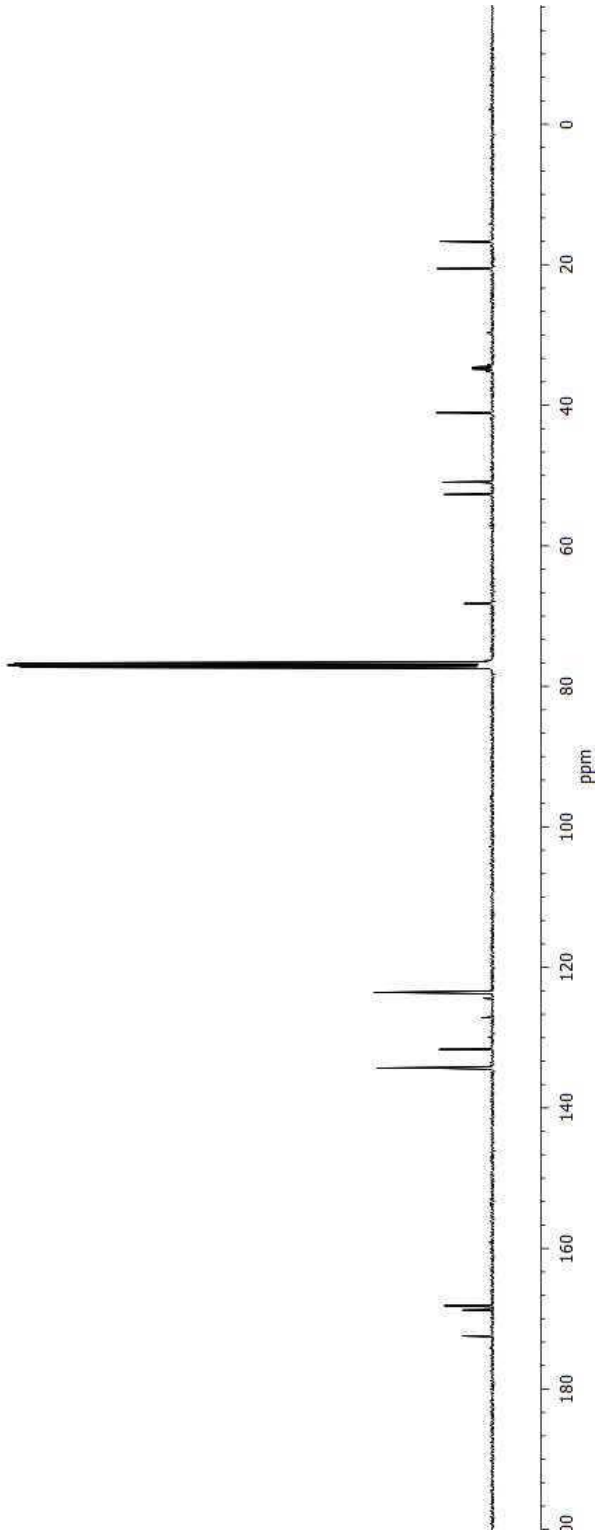
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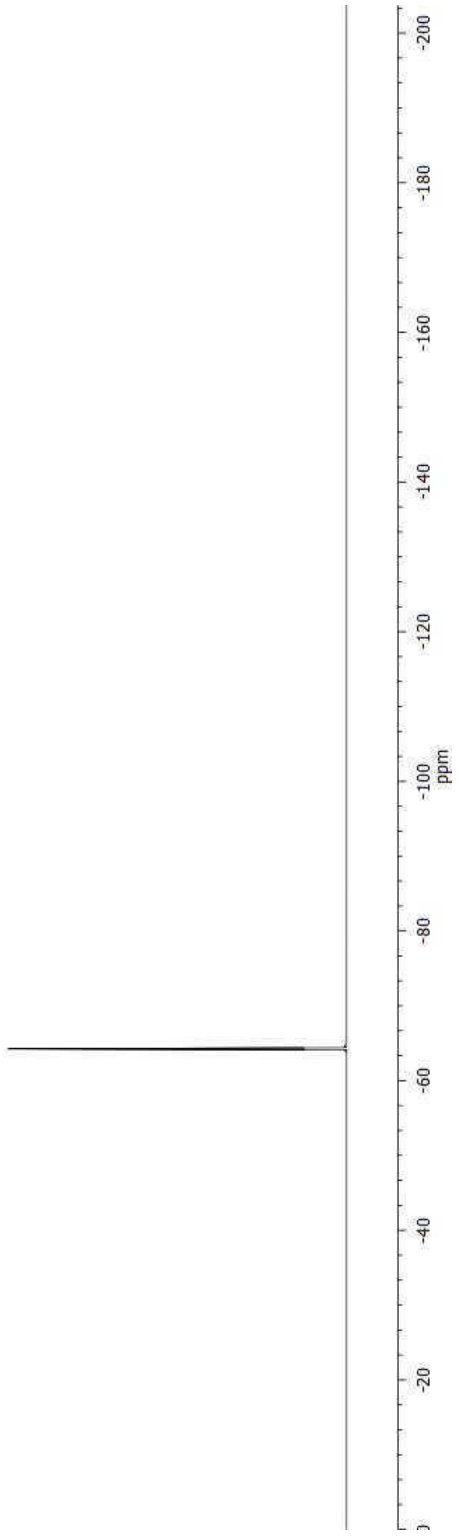
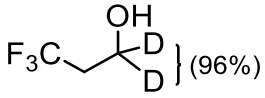


1,1,-dideuterio-3,3,3-trifluoropropan-1-ol (***deuterio*-6.1b**)



In modification to literature procedure,[116] a 50 mL round-bottom flask was charged with 5% ruthenium on carbon (2.6 g, 100 wt%), 3,3,3-trifluoropropan-1-ol (2 mL, 22 mmol, 100 mol%), and deuterium oxide (22 mL, 1.0 M). Under 1 atm of hydrogen gas, the reaction mixture was allowed to stir for 24 hours at 80 °C and then cooled to ambient temperature. The reaction mixture was filtered over a pad of Celite topped with sand. The filtrate was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with H_2O (15 mL), brine (15 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was then re-subjected to the above conditions, furnishing the title compound (1.1 g, 43%) as a yellow oil. The extent of deuterium incorporation was determined in the isolated product by integration of the corresponding signals in ^1H NMR (400 MHz, $CDCl_3$) and ^2H NMR (77 MHz, $CHCl_3$) and HRMS of the corresponding tosylate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (t, *J* = 6.2 Hz, 0.08H), 2.38 (q, *J* = 10.8 Hz, 2H), 1.90
(s, 1H).

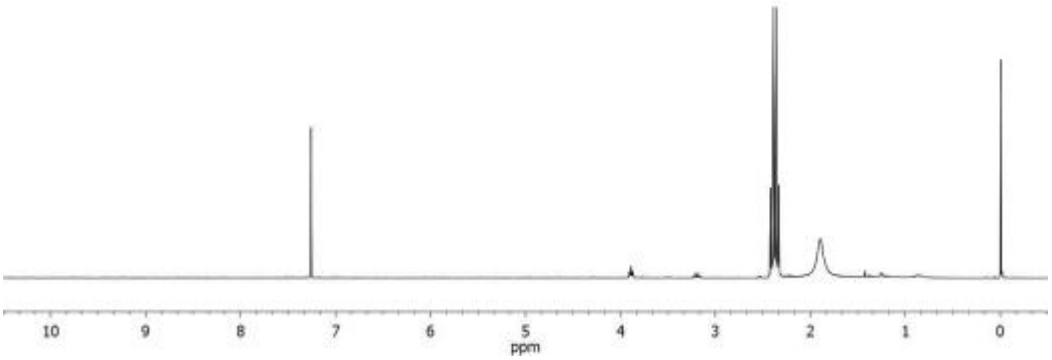
^{2}H NMR (77 MHz, $CDCl_3$): δ 3.88 (s, 1.92H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 126.4 (q, *J* = 276.3 Hz), 55.5 (t, *J* = 22.3 Hz), 36.5 (q, *J* = 27.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -64.6 (t, *J* = 10.9 Hz).

LRMS (EI): m/z 33 $[M\text{-}CH_2CF_3+H]^+$

FTIR (neat): 3356, 2120, 1733, 1433, 1369, 1262, 1128, 1092, 1066, 978, 923, 886, 847, 660 cm^{-1}.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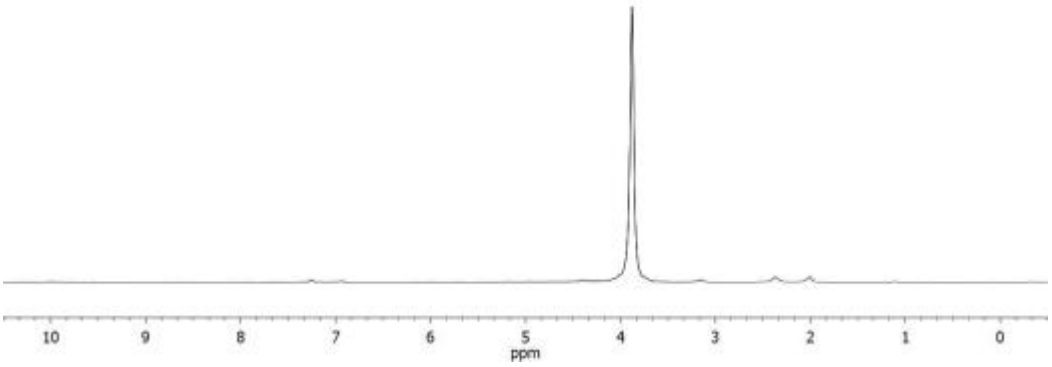
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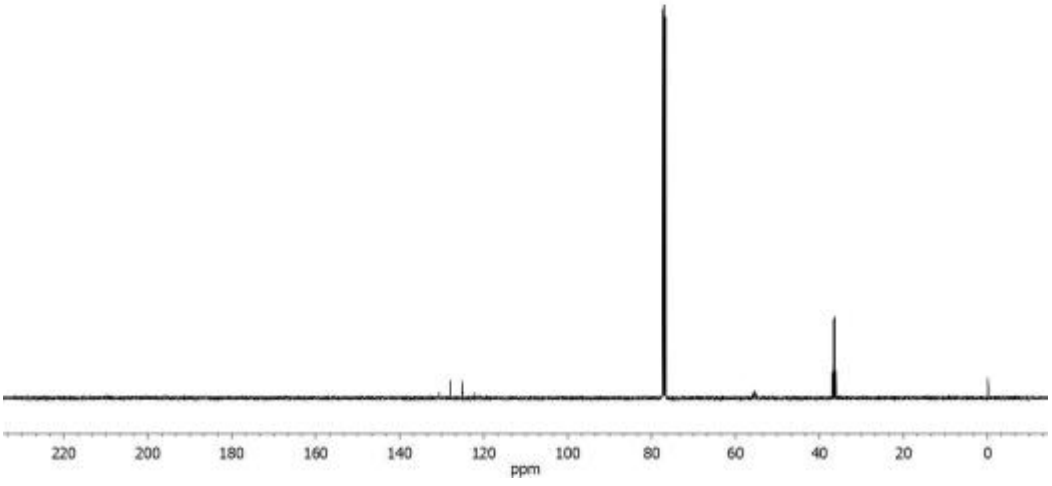
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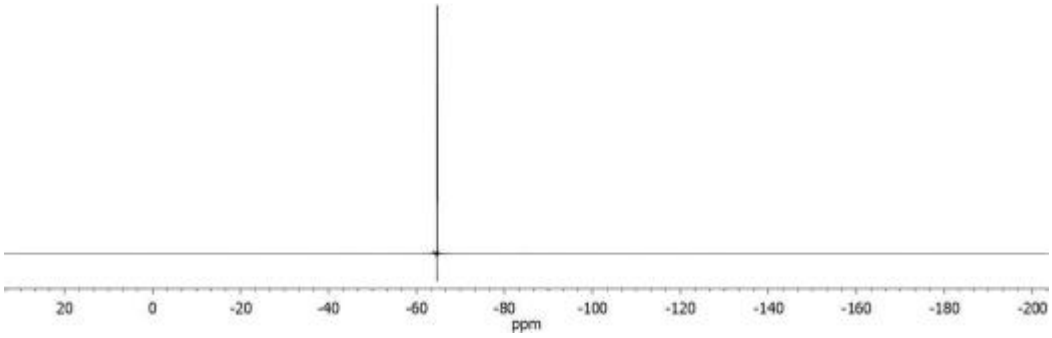
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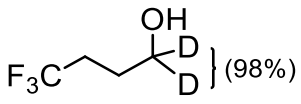
1,1,-dideuterio-4,4,4-trifluorobutan-1-ol (*deuterio*-6.1c)



In modification to literature procedure,[116] a 50 mL round-bottom flask was charged with 5% ruthenium on carbon (0.3 g, 50 wt%), 4,4,4-trifluorobutan-1-ol (0.6 g, 5 mmol, 100 mol%), and deuterium oxide (10 mL, 0.5 M). Under 1 atm of hydrogen gas, the reaction mixture was allowed to stir for 24 hours at 80 °C and then cooled to ambient temperature. The reaction mixture was filtered over a pad of Celite topped with sand. The filtrate was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with H_2O (15 mL), brine (15 mL), and dried over $MgSO_4$. After evaporation of solvents, the residue was then re-subjected to the above conditions, furnishing the title compound (0.27 g, 44%) as a colorless oil. The extent of deuterium incorporation was determined in the isolated product by integration of the corresponding signals in ^{1}H NMR (400 MHz, $CDCl_3$) and ^{2}H NMR (77 MHz, $CHCl_3$) and HRMS of the corresponding tosylate.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 – 3.66 (m, 0.05H), 2.29 – 2.14 (m, 2H), 1.84 – 1.76 (m, 1.94H), 1.33 (s, 1H).

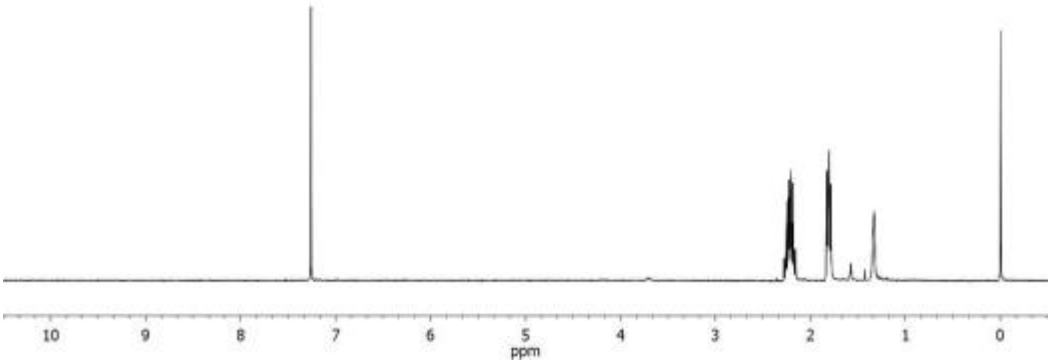
^{2}H NMR (77 MHz, $CDCl_3$): δ 3.69 (s, 1.95H), 1.79 (s, 0.06H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 127.3 (q, J = 275.8 Hz), 61.1, 30.3 (q, J = 28.6 Hz), 24.8 (q, J = 2.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -66.4 (t, J = 11.0 Hz).

LRMS (EI): m/z 33 $[M\text{-}CH_2CF_3+H]^+$

FTIR (neat): 3336, 2956, 1454, 1389, 1336, 1312, 1252, 1139, 1076, 1063, 1019, 1002, 968, 899, 849, 834 cm^{-1}.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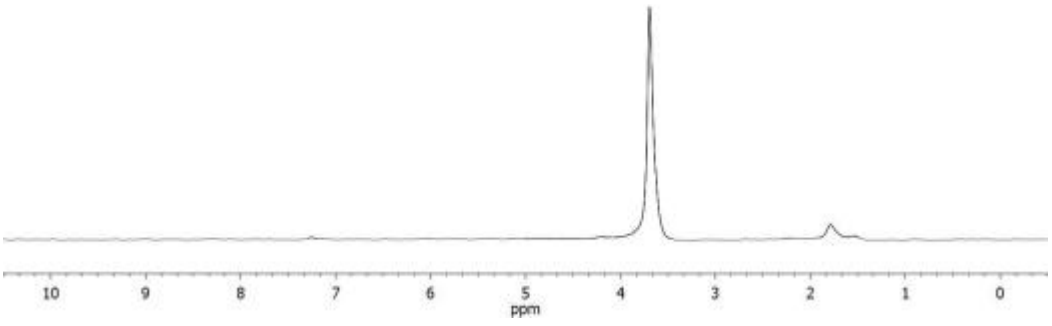
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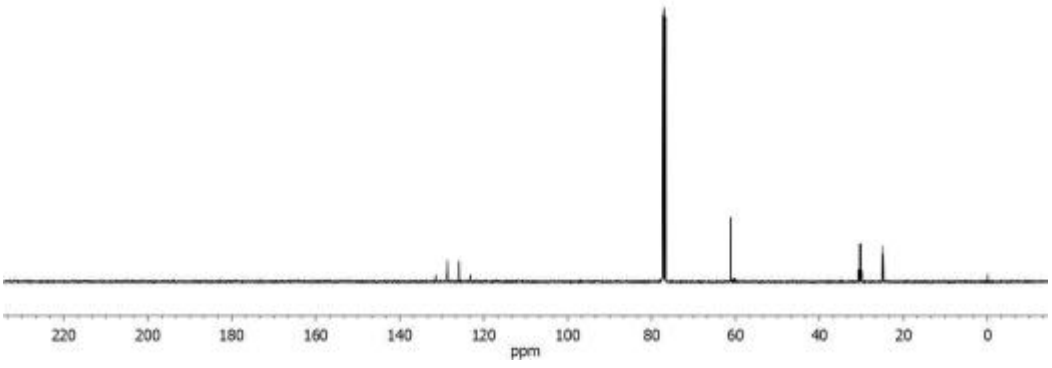
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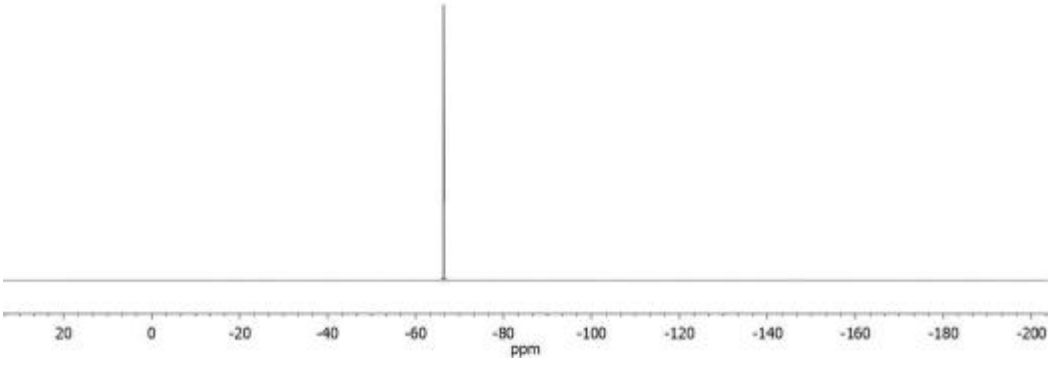
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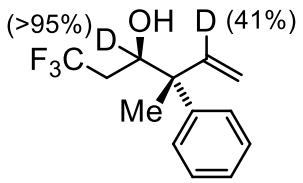
General Procedure B for the coupling of *deuterio*-alcohols to allene (6.2a)

To an oven-dried pressure tube equipped with magnetic stir bar was added $RuHCl(CO)(PPh_3)_3$ (9.5mg, 0.010mmol,5mol%),1,1'-bis(diisopropylphosphino)ferrocene (DiPPF) (4.2 mg, 0.010 mmol, 5 mol%), and alcohol (0.200 mmol, 100 mol%). The tube was sealed with a rubber septum, purged with argon, and THF (0.2 mL, 1.0 M with respect to alcohol) and allene **6.2a** (78 mg, 0.600 mmol, 300 mol%) were added. The rubber septum was quickly replaced with a screw cap and the reaction was heated to 75 °C for 48 hours. The reaction mixture was allowed to cool to room temperature, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2) to furnish the title compounds with yields averaged over two trials. The extent of deuterium incorporation was determined in the isolated product by integration of the corresponding signals in ^1H NMR (400 MHz, $CDCl_3$) and ^2H NMR (77 MHz, $CHCl_3$), averaged over two trials.

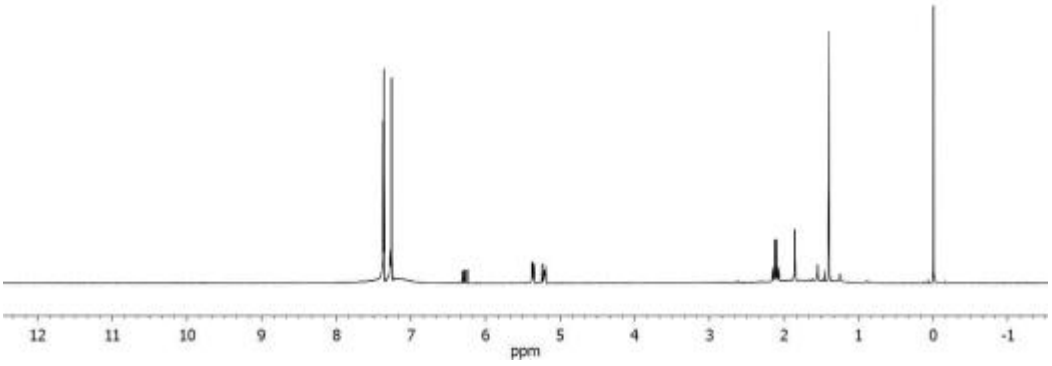
1,1,1-trifluoro-4-methyl-4-phenylhex-5-en-3-ol (*deuterio*-6.3b)



The reaction was conducted in accordance with **General Procedure B** *via* ***deuterio*-6.1b** (100 mol%). The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (8.3 mg, 17%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.29 – 7.22 (m, 1H), 6.28 (dd, J = 17.7, 10.9 Hz, 0.59H), 5.35 (dd, J = 10.9, 1.0 Hz, 1H), 5.21 (dd, J = 17.7, 1.0 Hz, 1H), 2.20 – 2.04 (m, 2H), 1.91 (dt, J = 3.1, 0.8 Hz, 1H), 1.39 (s, 3H).

^{2}H NMR (77 MHz, $CDCl_3$): δ 6.33 (s, 0.41 ^{2}H), 4.35 (s, 1 ^{2}H).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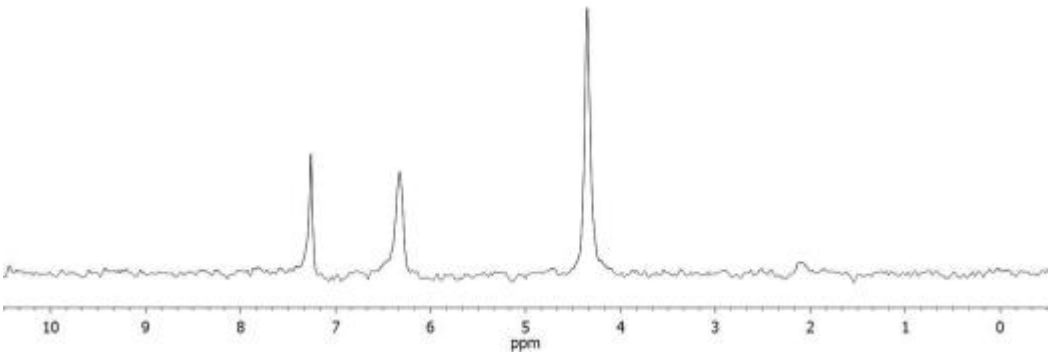
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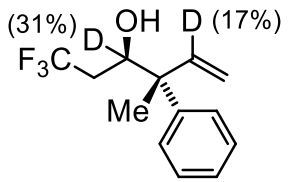
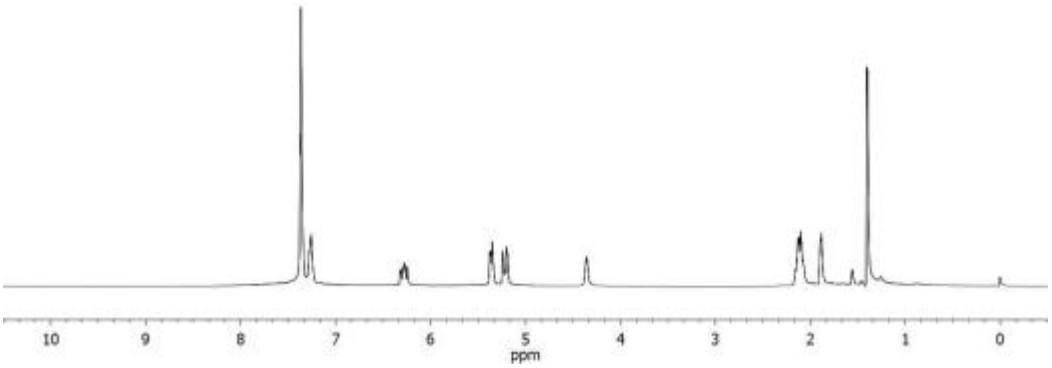
1,1,1-trifluoro-4-methyl-4-phenylhex-5-en-3-ol (*deuterio*-6.3b')



The reaction was conducted in accordance with **General Procedure B** *via* a 1:1 mixture of ***deuterio*-6.1b** : **6.1b** (100 mol%). The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (26.9 mg, 55%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.33 (m, 4H), 7.29 – 7.22 (m, 1H), 6.28 (dd, *J* = 17.7, 10.9 Hz, 0.83H), 5.35 (dd, *J* = 10.9, 1.0 Hz, 1H), 5.21 (dd, *J* = 17.7, 1.0 Hz, 1H), 4.40 – 4.30 (m, 0.69H), 2.20 – 2.04 (m, 2H), 1.91 (dt, *J* = 3.1, 0.8 Hz, 1H), 1.39 (s, 3H).

^{2}H NMR (77 MHz, $CDCl_3$): δ 6.33 (s, 0.17 ^{2}H), 4.35 (s, 0.31 ^{2}H).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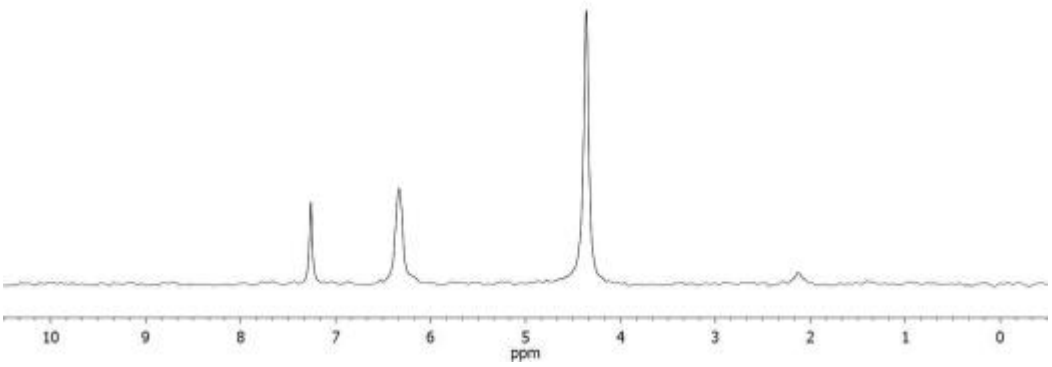
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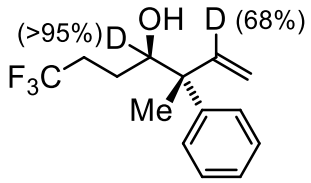
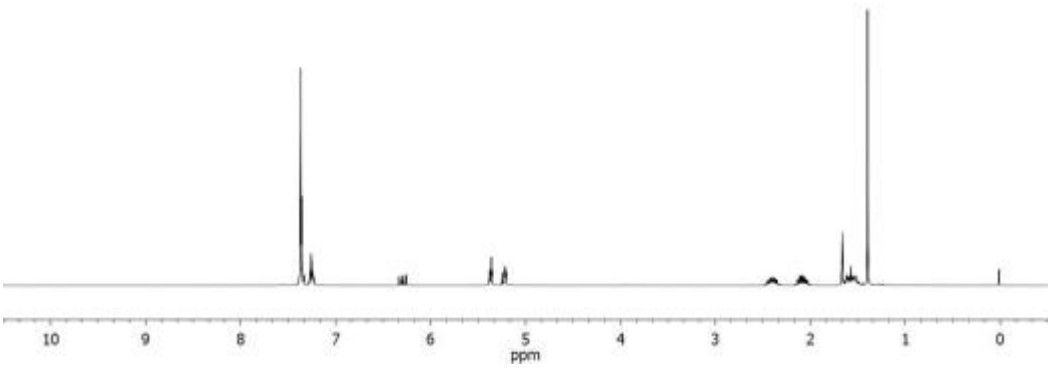
7,7,7-trifluoro-3-methyl-3-phenylhept-1-en-4-ol (*deuterio*-6.3c)



The reaction was conducted in accordance with **General Procedure B** *via* ***deuterio*-6.1c** (100 mol%). The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (44.9 mg, 87%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 4H), 7.28 – 7.21 (m, 1H), 6.28 (dd, *J* = 17.7, 10.9 Hz, 0.32H), 5.35 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.21 (dd, *J* = 17.7, 1.1 Hz, 1H), 2.49 – 2.29 (m, 1H), 2.16 – 1.96 (m, 1H), 1.69 – 1.65 (m, 1H), 1.65 – 1.43 (m, 2H), 1.39 (s, 3H).

^{2}H NMR (77 MHz, $CDCl_3$): δ 6.33 (s, 0.68H), 3.93 (s, 1H).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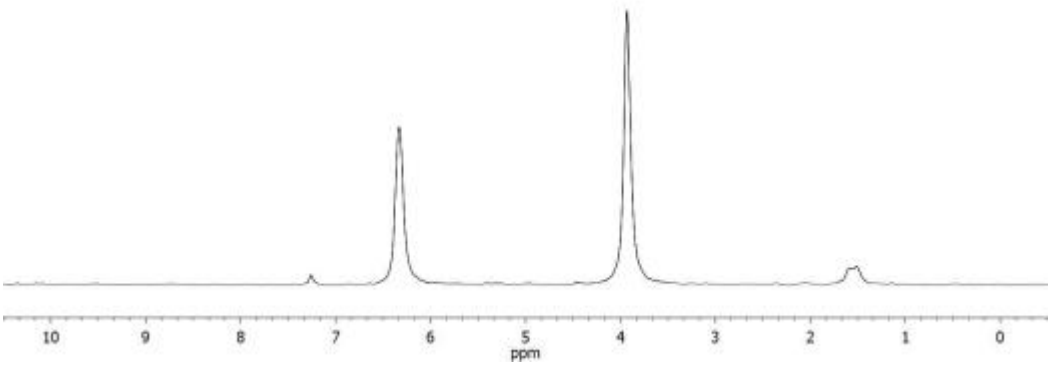
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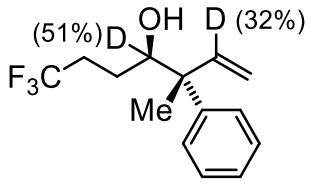
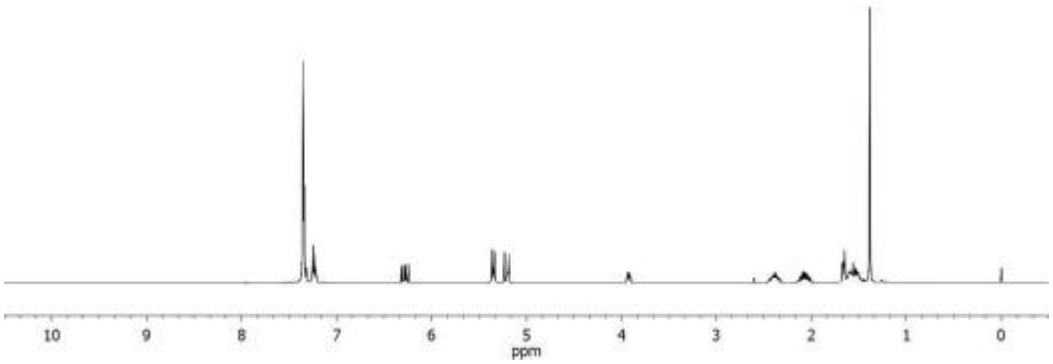
7,7,7-trifluoro-3-methyl-3-phenylhept-1-en-4-ol (*deuterio*-6.3c')



The reaction was conducted in accordance with **General Procedure B** *via* a 1:1 mixture of ***deuterio*-6.1c** : **6.1c** (100 mol%). The mixture was allowed to cool to room temperature, at which point the mixture was concentrated *in vacuo* and the residue was subjected to flash column chromatography (SiO_2, 3% EtOAc/hexane) to furnish the title compound (46.5 mg, 90%, >20:1 *dr*) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.31 (m, 4H), 7.28 – 7.21 (m, 1H), 6.28 (dd, *J* = 17.7, 10.9 Hz, 0.68H), 5.35 (dd, *J* = 10.9, 1.1 Hz, 1H), 5.21 (dd, *J* = 17.7, 1.1 Hz, 1H), 3.93 (dt, *J* = 10.5, 2.8 Hz, 0.49H), 2.49 – 2.29 (m, 1H), 2.16 – 1.96 (m, 1H), 1.69 – 1.65 (m, 1H), 1.65 – 1.43 (m, 2H), 1.39 (s, 3H).

^{2}H NMR (77 MHz, $CDCl_3$): δ 6.33 (s, 0.32H), 3.93 (s, 0.51H).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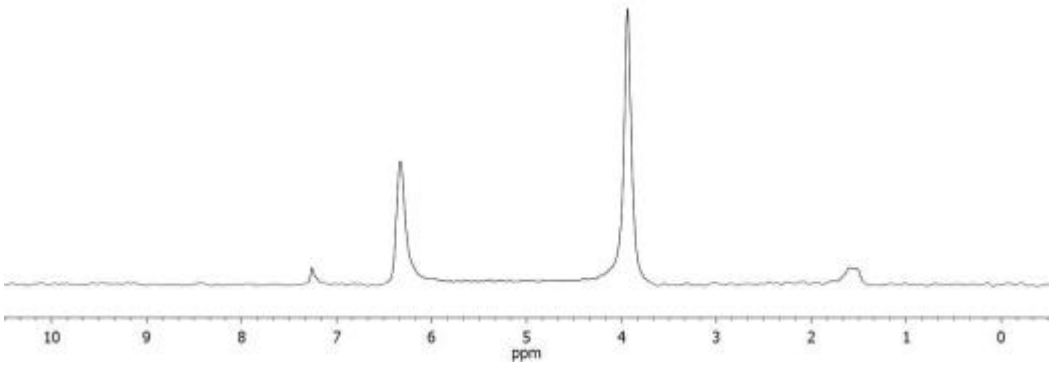
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